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DISSEMINATED PULMONARY CALCIFICATION*

Its Association with a Positive Reaction to Histoplasmin Antigen

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BOSTON

ANTIGEN skin testing in the presence of disseminated pulmonary calcification shows a high prevalence of histoplasmin sensitivity. Furcolow et al.,[1] in a combined study using tuberculin and histoplasmin antigen and x-ray examination of thousands of persons, begun in 1945 in Kansas City, Missouri, brought out the striking relation between calcifications seen on the roentgenograms and parallel skin sensitivity to the antigen. Table 1 illustrates the calcification-antigen relation observed in the Kansas City study.

Previous reports by Christie and Peterson[2] and Palmer[3] called attention to the frequency of histoplasmin sensitivity among negative tuberculin reactors whose films show disseminated pulmonary calcification. Palmer[4] also pointed out that a particular geographic origin of residence in a given group of people parallels a large number of histoplasmin-sensitivity reactions among them. These observations were based upon a study of several thousand student nurses among whom the greatest incidence of positive reactors to histoplasmin antigen coincided with their residential origin bordering the Mississippi Delta, especially east of the river.

During more recent years, however, the epidemiologic investigations of Grayston and Furcolow[5] and Furcolow and Grayston[6] indicate that point sources of infection with *Histoplasma capsulatum* are found in localities other than the Mississippi area. In 1 such case report originating in Vermont[7] the probable source of infection was considered to be the soil dust contaminated by chicken excreta. We postulate that the patient, a native Vermonter who had never left his home state, inhaled the spores of *H. capsulatum* while he was cleaning out chicken houses as a part of his daily farm chores.

Emmons[8] stresses the fact that this fungus is found more frequently in soil contaminated by chicken excreta than by any other source of infection. This suggests strongly that the chicken acts as a vector, polluting the soil constantly with the mycotic organism. In this connection it is of interest to consider factors that make for more frequent contamination with *H. capsulatum* in one type of soil than in another, even in localities that are known to have a high prevalence of histoplasmin sensitivity, such as Williamson County, Tennessee, as reported by Zeidberg et al.[9] These investigators have studied the problem from the physiochemical point of view, and have pointed out the greater prevalence of the fungus in soil contaminated by chicken excreta, confirming the observations of Emmons, and the fact that soil from which *H. capsulatum* had been isolated had an appreciably higher acidity than negative soil. The writers point out that in the laboratory *H. capsulatum* is capable of abundant growth over a wide range of pH. Under natural conditions, however, the level of pH appears to be more vital. They postulate that the soil may act by inhibiting certain competitors rather than by enhancing the growth of the fungus directly. Finally, it has been shown that in areas of highest prevalence of histoplasmin sensitivity the soil is characteristically acid, reported by Zeidberg.[10]

In an analysis of a number of histoplasmosis epidemics, Grayston and Furcolow[5] have called attention to the shoveling of the excreta of chickens, pigeons and bats, when the shovelers raise a cloud of dust cleaning out chicken houses, abandoned buildings and church belfries, as a suitable process for the inhalation of the *H. capsulatum* spores.

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Material and Method

Since the end of World War II a number of veterans have appeared in the Chest Section of the Outpatient Department for the purpose of determining the significance of certain abnormalities that had been noted on the chest roentgenograms during service or at the time of separation. We were intrigued to note disseminated calcification in these young, obviously healthy veterans. We considered the abnormalities the end result of previously active histoplasmosis in the lungs (Fig. 1).

TABLE 1. *Calcification-Antigen Relation.*

Antigen	Reaction	Rate of Calcification Incidence
		%
Histoplasmin	Negative	5
Tuberculin	Negative	
Histoplasmin	Negative	17
Tuberculin	Positive	
Histoplasmin	Positive	30
Tuberculin	Negative	

The unusual pattern of these abnormal shadows is attested to by the variety of designations given these residual lesions when they were first noted in the service hospital or discharging station, such as "healed miliary tuberculosis," "sarcoidosis," "pneumoconiosis," "miliary calcifications" and "arrested tuberculosis."

We have studied in considerable detail 20 cases of disseminated calcification and determined the following information: birthplace and residence before service; findings on the induction films; exposure to soil dust before service; history of respiratory illness before or during service; whether the veteran was an integral part of a respiratory-disease epidemic; whether mycotic infection was considered at the time of interpretation of the roentgenograms during service; and whether they could currently react to the conventionally used triad of antigens — namely, *tuberculin, coccidioidin and histoplasmin.* Lastly, in 15 cases, determination was made whether antibodies were still present in the blood serum.

Observations

Birthplace and residential origin of the patients were as follows: Indiana, 2; Missouri, 2; Iowa, 2; Kentucky, 1; Ohio, 1; and Illinois, 1. One lived in succession in Mississippi, Tennessee and Arkansas. Thus, 10 patients were from the central, or endemic, states. The other 10 had the following residential origin: 8 spent their entire lives in Massachusetts, 1 in Pennsylvania, and 1 in Rhode Island. Of the entire group analyzed, 10 had not had respiratory infections in childhood or adult life. Two of these 10, however, gave a history of massive inhalation of soil dust for several years before entering service while working as laborers in the central states of which they were natives. The other remaining 10 gave a history of respiratory infection of which 8 could not be pinpointed on details. We were rewarded in our study, however, when we learned that 2 of the latter group, Massachusetts natives, were components of the Camp Gruber, Oklahoma, epidemic of 1944, reported as an "unusual disease" by Cain et al.[11] The epidemic was studied by Furcolow and Grayston,[5] who stressed the fact that accumulated evidence pointed to histoplasma as the etiologic agent of that epidemic (Fig. 1).

In performing the antigen skin tests we obtained data based on the testing of 18 persons. Table 2 shows our findings. It was not possible to test each of the 20 patients with all three selected antigens. Moreover,

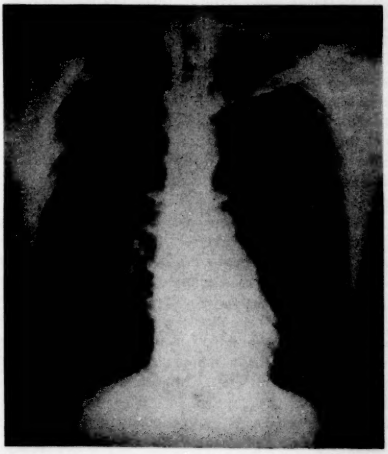

FIGURE 1. *Roentgenogram of a Native of Massachusetts Whose Induction Films Were Normal.*
This case was a component of the Camp Gruber respiratory-disease epidemic of 1944. Military-hospital records indicated diffuse bilateral mottling (x-ray films not available). Note that the current disseminated pulmonary calcification was unchanged during our observation period.

since our primary interest was the presence of a positive histoplasmin antigen skin test in each case tested, we considered tuberculin and coccidioidin reactions incidental observations.

We next reviewed the interpretations of the x-ray films taken by the service hospital or discharging station. Various diagnostic terms used to describe the lesions are quoted herewith: "healed miliary tuberculosis" (3 cases); "pneumoconiosis" (2 cases); "sarcoidosis" (1 case); "miliary calcification" (1 case); "hamartoma" (1 case); "spots in the lungs" (1 case);

"arrested tuberculosis" (1 case); "bilateral calcified deposits" (1 case); "fungous infection" (1 case); "healed primary tuberculosis" (1 case); "healed primary complex" (1 case); and "histoplasmosis" (3 cases). It is interesting that the likelihood of the last-named infection was not considered frequently. Furthermore, the 2 cases that were components of the Gruber epidemic were described as "interstitial pneumonitis" even during the later phase of the convalescence period when disseminated nodulation had become evident.

TABLE 2. *Results of Antigen Skin Tests in 18 Cases.*

ANTIGEN	POSITIVE REACTORS	PERSONS TESTED
Tuberculin	9	18
Coccidioidin	1	15
Histoplasmin	18	18

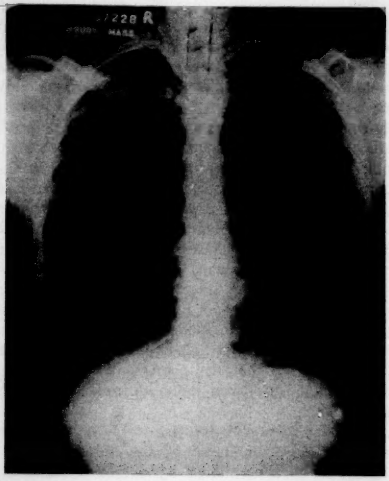

FIGURE 2. *Roentgenogram of a Native of Jamaica, British West Indies, Who Lived on a Chicken Farm, Actively Engaged in Its Operation, until Fifteen Years of Age. Induction films were not available. Note the mass of calcified lymph nodes in the left hilar region.*

The serums of 15 patients were studied in search for the presence of antibodies. We were indeed surprised to find that the serum of 1 showed a 1:4 reaction when the yeast-phase antigen of *H. capsulatum* was titrated against it. The serum of a second patient when standard *H. capsulatum* antigen was titrated against it showed a 1:14 reaction. All the others tested showed no serum antibodies. In a personal communication, Dr. Furcolow regarded the 1:4 titer as a "doubtful" reaction, whereas the titer of 1:14 he considered a "positive" reaction. The first case was a component of the Gruber epidemic; the second patient was stationed in Tennessee for five months, during which he was hospitalized for five days because of an acute "bronchitis." No x-ray examinations were made during the acute or convalescent phase of the infection.

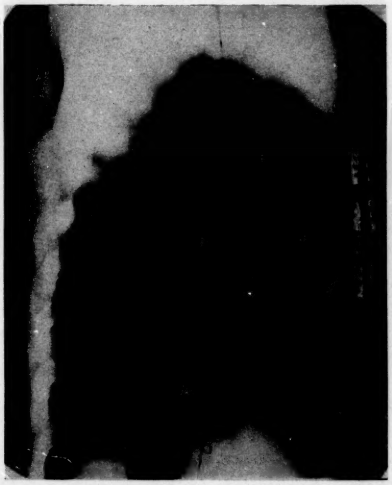

FIGURE 3. *Lateral Laminagram, Showing the Hilar Mass of Lymph Nodes.*

We next ascertained the frequency of disseminated calcification seen on the induction films of the group studied. Seven patients had no disease; this information was not available in 6; whereas 7 showed disseminated calcification on induction. The last group resided in endemic areas before induction. Finally, none of these patients ever had symptoms referable to the respiratory system during the entire period of observation, which extended between 1946 and 1954.

DISCUSSION

The first report of a case of infection with *H. capsulatum* was made by Darling[12] in 1906. He described lesions that he called "pseudotubercles" in the lungs, liver and spleen, and characterized the infection as one in which there were fever, splenomegaly and emaciation. Obviously, he was describing the disseminated, fatal form of the disease. Indeed, for many years thereafter, this mycotic infection was looked upon as fatal. In 1940, however, Meleney[13] called attention to the occurrence of benign histoplasmosis ap-

parently focalized in the lungs alone. It is of considerable interest that on purely theoretical grounds Smith[14] postulated, in 1943, that histoplasmosis might be the cause of pulmonary calcification in negative tuberculin reactors in certain areas of the United States. Thus, the ground was prepared for further

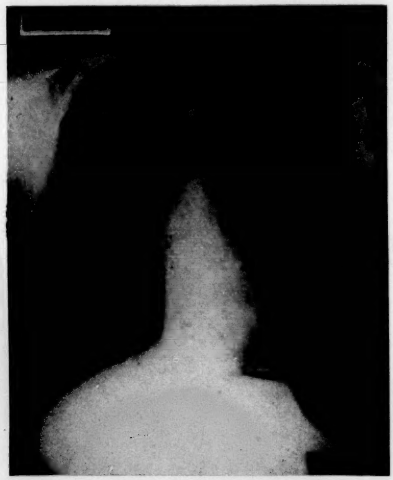

FIGURE 4. *Roentgenogram Taken on Separation from the Service of a Patient Who Was Considered to Have a "Coin" Lesion That Was Thought to Be Due to a Tuberculoma. Tuberculin antigen skin tests were reportedly negative, and the histoplasmin antigen tests consistently positive. Training was in an endemic area. Note the round lesion, with central calcific stippling overlying the middle portion of the sixth left anterior rib.*

study regarding the relation between the large number of positive histoplasmin skin tests and parallel pulmonary calcifications occurring among residents of a particular zone of the United States. In this manner the endemic character of the infection with *H. capsulatum* became clear.[3,4]

The roentgenologic appearance of the lesions of histoplasmosis depends upon the phase of the infection. A pneumonitis is the most common early manifestation. Rarely is the pathology limited to the hilar lymph nodes alone. Conversely, about three fourths of the patients with parenchymal infiltration show involvement of these nodes as well. The pneumonic infiltrate consists of single but more often multiple patches of consolidation. As the infection resolves, some of the infiltrates disappear quickly whereas others persist for longer periods. After a while scattered nodulations appear accompanied by calcium deposition within them.

The evolutionary phases of the infectious process are described in an interesting study by Sontag and Allen[15] in a group of children known to be infected with *H. capsulatum*. The initial x-ray study showed patches of bronchopneumonia, diffusely scattered and predominantly at the bases. After varying periods the authors noted the appearance of disseminated calcifications, which became manifest usually soon after the initial lesions had resolved. It was further observed that in some cases the calcification process is actively progressive, suggesting strongly that the organism in the lungs may remain active for long periods. We wish to postulate, therefore, that antibody activity for long periods, as noted in 2 of our cases, represents a chronic infection of an active nature pathologically, although the patients appear well clinically. We believe that the infection in these 2 cases dates back twelve years and eleven years respectively.

Differential diagnosis in primary histoplasmosis should consider bacterial and viral pneumonia, Loeffler's pneumonia, tuberculosis and neoplastic infiltration. In the 2 cases that were part of the epidemic alluded to above, studies performed many months after the initial phase of the illness were regarded as showing "interstitial pulmonary fibrosis." The possibility of histoplasmosis was not entertained at that time.[11]

An important etiologic factor in the occurrence of the infection described by Furcolow and Grayston[5] concerns the mechanism of the inhalation of the spores of *H. capsulatum*. They stress the fact that infection can easily take place when those working in a cloud of dust created during the process of cleaning out hen houses, abandoned school buildings and church belfries are exposed to spore-laden, pulverized excreta of hens, pigeons and bats. Their epidemiologic studies further indicate that the point source of infection could well be in places removed from the central-states area.

The hilar adenopathy accompanying histoplasmosis is a common denominator of any form of the parenchymal infection. These nodes may be unilateral or bilateral and may vary in size and number, and there is no specific manner in which they calcify. Involvement of the hilar lymph nodes without parenchymal lesions is very uncommon. In our study we were especially interested in this phase of the infection since we wished to determine whether involvement of the nodes is paralleled by positive antibody titers in the serum, as stressed by Furcolow and Grayston in their observations of acute and subacute phases of the infection. According to these investigators, antibodies are apt to be present more often when the hilar lymph nodes are involved, especially during the acute and subacute phases of the infection. From their analysis of a number of histoplasmosis epidemics they concluded that complement-fixation and precipitin tests for *H. capsulatum* infection showed high titer reactions in most of those serums obtained within three

months of the onset of the epidemic, with falls in titer thereafter. The serums in the Gruber epidemic showed after seven years the following complement-fixing titer values: 2 positive, 10 doubtful and 10 negative. As we had expected, no precipitins were demonstrated. Furthermore, it was noted that precipitins appear early and disappear rapidly, whereas complement-fixing antibodies are identified later and persist for a relatively long time. Therefore, when we observed pertinent findings in only 2 of the cases tested — namely, a reaction of 1:4 and 1:14 when the serum was titrated against the yeast phase, or standard antigen of *H. capsulatum*, respectively — this fact was not viewed by us with any degree of surprise. It should be stressed, however, that Dr. Furcolow, in a personal communication, considered the case in which the titer was 1:14 as denoting considerable residual histoplasmosis activity. Regarding the hilar-adenopathy component in the 2 cases just described, Case 1 showed enlargement of the hilar nodes during the period of illness and several large calcified lymph nodes were present bilaterally throughout the entire period of observation in the clinic. The patient showing a 1:14 titer had similar findings.

In cases of histoplasmosis limited to the hilar nodes, differential diagnosis should include sarcoidosis, tuberculosis, blastomycosis, coccidioidomycosis, lymphoma, erythema nodosum, infectious mononucleosis and certain pneumoconioses. The presence of calcification within these nodes helps to narrow down the diagnostic possibilities (Fig. 2 and 3).

The case referred to above (Fig. 2 and 3) was observed during the past year. The patient came to the attention of the clinic for the purpose of determining the significance of the abnormal shadow in the perihilar region. The lesion was noted on an x-ray film taken on separation from the service and was considered due to a vascular anomaly. Considerable investigation did not confirm this impression. Up to the time of his observation in this clinic the possibility of residual histoplasmosis was not entertained. We determined that he had lived on a chicken farm in Jamaica till the age of fourteen and had been participating actively in its operation. We therefore postulated that he could have become infected with *H. capsulatum* because of the exposure to soil contaminated by chicken excreta. Antigen skin testing showed on two separate occasions negative tuberculin and positive histoplasmin reactions. The serum was examined for complement-fixing antibodies, but none were identified.

Another variety of histoplasmosis lesion, the round, granulomatous infiltrate commonly designated as the "coin" type of lesion, is encountered in the inactive but sometimes, less frequently, also in the active phase of the infection, with or without central calcification. It is usually single, but more than one lesion may be present. Differential diagnosis should include tuberculosis (tuberculoma) and coccidioidomycosis as well as other fungi in addition to hamartoma and other primary or metastatic tumors (Fig. 4).

Cavitary lesions in histoplasmosis have been reported but are rare.[16-18] When confined to an upper lobe they can easily be confused with tuberculosis. In

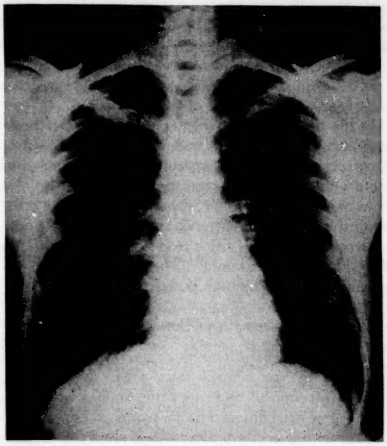

FIGURE 5. *Roentgenogram of a Native of Iowa Whose Induction Film Was Normal.*

He had had a respiratory infection while in the service; no x-ray films were available for that period. Note the minute, disseminated calcification accompanied by lymph-node calcification in the hilar regions. Tuberculin antigen was repeatedly negative; and histoplasmin tests repeatedly positive.

1 case[16] the patient was an itinerant day laborer who did considerable farm work. He never left his native state of New York. X-ray examination of the chest showed chronic granulomatous infiltration in each upper lobe, with bilateral cavitation, and he had varied and repeated hemoptyses. The sputum disclosed elastic tissue, and *H. capsulatum* was cultured with ease. No tubercle bacilli were ever isolated. Up to 1950 only 4 cavitary cases had been reported. Of these, 3 were treated by lobectomy. The cavity in histoplasmosis has no pathognomonic features. Differential diagnosis besides tuberculosis should include abscess, neoplasm, cysts and other mycotic infections.

The most commonly observed chronic lesion in histoplasmosis is the one showing disseminated calcified nodules. It represents the arrested phase of the initial infection. The individual nodules vary in number from a few to hundreds and are usually 1 to 5 mm. in size. Furcolow and Grayston[6] designate them as "disseminated miliary" when they are very small, numerous and scattered uniformly throughout the lungs and as "multiple" when fewer, more localized

calcifications are present. The type of lesion just described is accompanied by hilar adenopathy in about three fourths of the cases reported by various observers. Our series of 20 cases parallels this observation, 15 of the group showing hilar adenopathy. When the individual calcified nodule is observed, it is noteworthy that progressive shrinkage and calcium deposition, especially in its central portion, are the outstanding features. In the diffuse, disseminated type of infiltration, differential diagnosis should include broncholithiasis, diffuse bronchiectasis, pulmonary edema, neoplastic miliary metastasis, primary miliary adenomatosis and microlithiasis of the alveoli.

In the final analysis, when residual lesions of histoplasmosis are considered, neither the hilar distribution of adenopathy nor the granulomatous parenchymal lesion will ordinarily arouse the examiner's suspicion of an old infection with *H. capsulatum*. On the other hand, the finding of scattered areas of calcified nodular density in the lung fields readily arouses a suspicion of residual histoplasmosis. The roentgenologic appearance of these nodules is striking (Fig. 5).

Summary and Conclusions

Infection with *Histoplasma capsulatum* occurs most frequently in the central-states area. Nevertheless, possible infection in other localities should be kept in mind when the clinical history points to exposure to dust contaminated by the excreta of chickens, pigeons and bats. Residua of the infection may be located in hilar lymph nodes or may be seen as a granulomatous lesion in the lung, but are most commonly found as disseminated calcification in a portion of a lung or, more frequently, throughout the entire parenchyma.

Antigen skin testing is paramount in differentiating infection due to *Mycobacterium tuberculosis* and *H. capsulatum*. Although complement-fixing antibodies are seldom demonstrated many years after the initial infection, it is important to examine the serum of suspected cases.

In a group of cases reported, the presence of antibodies was demonstrated in 2 cases twelve and eleven years after the initial episode of respiratory infection. In the first case, considered "doubtful," the titer was 1:4; in the second, considered "positive," the titer was 1:14.

It is significant that few patients showing residual histoplasmosis have any knowledge of experiencing serious respiratory illness in the past. Some are aware of past exposure to contaminated soil dust. Most of those with healed lesions have no knowledge of past respiratory disease.

The clinician and roentgenologist must maintain a high degree of suspicion if the presence of active but particularly inactive phases of infection with *H. capsulatum* is to be detected. The roentgenologic appearance of residua in the form of disseminated calcification is striking. The individual nodule has a sharpness of outline that is impressive. If it is kept in mind this disease is less likely to be confused with calcific nodulation from other causes.

We are indebted to Dr. Michael L. Furcolow, of the United States Public Health Service, for the data in Table 1, which are based upon his epidemiologic studies, and for permission to have our serum samples analyzed in the Public Health Service Laboratories. The co-operation of the Allergy Section of the Outpatient Clinic in the performance of the antigen skin tests is also acknowledged.

References

1. Furcolow, M. L., High, R. H., and Allen, M. F. Some epidemiological aspects of sensitivity to histoplasmin and tuberculin. *Pub. Health Rep.* **61**:1132-1144, 1946.
2. Christie, A., and Peterson, J. C. Pulmonary calcification in negative reactors to tuberculin. *Am. J. Pub. Health* **35**:1131-1147, 1945.
3. Palmer, C. E. Nontuberculous pulmonary calcification and sensitivity to histoplasmin. *Pub. Health Rep.* **60**:513-520, 1945.
4. *Idem.* Geographic differences in sensitivity to histoplasmin among student nurses. *Pub. Health Rep.* **61**:475-487, 1946.
5. Grayston, J. T., and Furcolow, M. L. Occurrence of histoplasmosis in epidemics — epidemiological studies. *Am. J. Pub. Health* **43**:665-676, 1953.
6. Furcolow, M. L., and Grayston, J. T. Occurrence of histoplasmosis in epidemics: etiologic studies. *Am. Rev. Tuberc.* **68**:307-320, 1953.
7. French, E. E., Jillson, O. F., and Crispell, L. C. Histoplasmosis in life-long resident of New England. *New Eng. J. Med.* **249**:270-272, 1953.
8. Emmons, C. W. Isolation of *Histoplasma capsulatum* from soil. *Pub. Health Rep.* **64**:892-896, 1949.
9. Zeidberg, L. D., Ajello, L., and Webster, R. H. Physical and chemical factors in relation to *Histoplasma capsulatum* in soil. *Science* **122**:33, 1955.
10. Zeidberg, L. D. Theory to explain geographic variations in prevalence of histoplasmin sensitivity. *Am. J. Trop. Med.* **3**:1057-1065, 1954.
11. Cain, J. C., Devins, E. J., and Downing, J. E. Unusual pulmonary disease. *Arch. Int. Med.* **79**:626-641, 1947.
12. Darling, S. T. Protozoön general infection producing pseudotubercles in lungs and focal necroses in liver, spleen and lymphnodes. *J.A.M.A.* **46**:1283-1285, 1906.
13. Meleney, H. E. Histoplasmosis (reticulo-endothelial cytomycosis): review with mention of 13 unpublished cases. *Am. J. Trop. Med.* **20**:603-616, 1940.
14. Smith, C. D. Coccidioidomycosis. *M. Clin. North America* **27**: 790-807, 1943.
15. Sontag, L. W., and Allen, J. E. Lung calcifications and histoplasmin-tuberculin sensitivity. *J. Pediat.* **30**:657-667, 1947.
16. Monroe, J., and Kurung, J. M. Histoplasmosis with review of literature and report of case, proved by culture, with involvement of upper lobe of each lung simulating active bilateral apical pulmonary tuberculosis. *Ann. Int. Med.* **38**:206-223, 1951.
17. Bettag, O. L. Pulmonary resection for histoplasmosis: case report. *J. Thoracic Surg.* **22**:434-438, 1951.
18. Peeples, W. J., and Spence, M. J. Pulmonary cavitation due to *Histoplasma capsulatum*. *Am. Rev. Tuberc.* **69**:111-115, 1954.

SURGICAL MANAGEMENT OF NEOPLASTIC PULMONARY METASTASES*

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BOSTON

THE increasing age of the population with the associated increased incidence of cancer, the increasing number of patients successfully operated upon for neoplastic disease and the larger number of routine chest survey roentgenograms are facts that tend to emphasize the importance of the growing problem of pulmonary metastatic disease.

The present state of perfection of the technics for the resection of pulmonary tissue, or the excision of tumors growing in the lung, no longer permits a defeatist attitude when the physician is faced with the problem of metastatic neoplastic deposits in the lungs. There is no gainsaying the fact that the problem is frequently an extremely knotty one, and that it is difficult to arrive at a decision about treatment not only because of the physical facts but also because of the intangible ones associated with a situation that heretofore was considered beyond help or even hope. There is a natural reluctance on the part of the physician to subject a patient to a procedure that may not help and may, under certain circumstances, make him more uncomfortable. However, the accumulated experience of recent years[1-3] should encourage the physician to consider active rather than passive measures when he is evaluating some of these patients for therapy.

An aggressive philosophy in dealing with neoplastic disease is encompassed by the knowledge, now amply confirmed, that single, or even multiple, pulmonary metastases are not necessarily prima-facie evidence of widespread extrapulmonary dissemination of the disease. It has been suggested statistically that in a person with one cancer a second primary tumor is more apt to develop; hence the radiographic demonstration of a shadow of increased density in the pulmonary field at any time after the apparently successful extirpation of a primary growth elsewhere may in fact indicate another primary tumor, which may be a benign one, as in 4 of the cases on which this report is based (Table 1). In 2 cases the tumors, thought to be metastatic from the breast, proved to be bronchial adenomas; 1 was a hamartoma, and another was a nonresectable primary adenocarcinoma of the lung. However, the likelihood of such occurrences will be governed, to a degree, by the natural history of the original tumor.[4]

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On the other hand, it is always possible that any demonstrable metastatic lesion is truly a solitary one, and its extirpation may result in cure. I am in complete accord with the philosophy of Minor,[4] who holds that it is obvious that there will be local recurrences or distant metastases after pulmonary resection in a certain number of patients, but this is not sufficient reason for withholding treatment that may add a significant number of cures. This is not to say that all patients should be operated upon. Obviously, there are certain criteria for selection.

METHODS OF SELECTION OF CASES

Status of the Primary Lesion

Before any consideration can be given to the excision of metastatic pulmonary lesions, the primary lesion shall have been apparently completely removed and there shall be no evidence of local recurrence. Rarely, in cases in which bleeding or sepsis is a fundamental consideration, it may be urgent to resect the metastasis first if the primary tumor seems resectable.

General Considerations

The evaluation of the general condition and cardiovascular apparatus common to all patients who are being considered candidates for thoracic operation requires no special comment. In general, age is not an important factor, other things being equal. Of great importance is the evaluation of the pulmonary function by the usual ventilatory studies, as well as bronchospirometry, when the possibilities of total pneumonectomy and bilateral resection are entertained. This is of particular importance in older patients, in whom pulmonary emphysema is often an integral part of the picture.

It is essential that every effort be made to exclude hopelessly disseminated disease. Laminagraphy of the lungs, bone-marrow biopsy, roentgenographic examination of the skeleton and acid and alkaline phosphatase determinations are used routinely in the evaluation of the patient before operation is decided on.

Natural History

Cognizance should be taken of the original lesion, as well as the distribution of the pulmonary metastases. Thus, as pointed out by Minor,[4] of 77 cancers of the breast metastasizing to the lung, there was also pleural involvement in 26, or 33.7 per cent, and involvement of the mediastinal lymph nodes in 23 per cent. This rate is higher than that for any other primary tumor, and consequently a patient with a "solitary" pulmo-

nary metastasis from cancer of the breast with pleural effusion seems an unlikely candidate for resection. At the other end of the spectrum, the well known propensity for hypernephroma to give solitary metastases with long-term survival after resection requires no additional comment.

There is no reason to withhold bilateral resection under similar circumstances if the two metastases occur and are recognized simultaneously. Other combinations of lobes or their segments, unilateral and bilateral, have been resected successfully with long-term or short-term survival (Cases 4 and 11, Table 1).

TABLE 1. *Total Operative Experience with 22 Resections of Pulmonary Tissue for Metastatic Disease in 20 Patients.*

CASE NO.*	SEX	AGE	TYPE & LOCATION OF PRIMARY LESION	INTERVAL BEFORE METASTASIS	DATE OF OPERATION	TYPE OF OPERATION	STATUS AT LAST FOLLOW-UP EXAMINATION
		yr.					
Patients alive:							
1	M	62	Renal carcinoma; right.	1st seen	March, 1946	Lobectomy (right middle lobe)	Patient well — 98 mo.
2	M	47	Adenocarcinoma; bladder.	4 yr.	February, 1949	Pneumonectomy (right)	Patient well — 81 mo.
3	F	65	Adenocarcinoma; uterus.	4 yr.	March, 1949	Lobectomy (left upper lobe)	Patient well — 80 mo.
4	F	38	Adenocarcinoma; colon.	5 yr.	December, 1949	Removal of segment of left upper lobe	Patient alive with disease — 71 mo.
				9 yr.	October, 1953	Lobectomy (left upper lobe)	
6	F	63	Adenocarcinoma; uterus.	7 yr.	January, 1951	Lingulectomy (left upper lobe)	Patient well — 58 mo.
8	M	53	Renal carcinoma	1st seen	July, 1951	Lobectomy (right lower lobe)	Patient well — 52 mo.
9	F	53	Leiomyosarcoma; uterus.	8 yr.	July, 1952	Wedge resection (right upper lobe)	Patient well — 40 mo.
10	F	61	Melanocarcinoma; eye.	25 yr.	December, 1952	Lobectomy (right middle & lower lobes)	Patient well — 12 mo.
16	F	60	Fibrosarcoma; breast.	8 yr.	May, 1954	Pneumonectomy (left)	Patient well — 18 mo.
17	F	60	Adenocarcinoma; breast.	6 yr.	June, 1954	Lobectomy (right lower lobe)	Patient alive with disease — 18 mo.
Patients dead:							
5	F	68	Carcinoma — left breast; thyroid carcinoma†; carcinoma — right breast.	12 yr.†	December, 1950	Wedge resection (right upper lobe)	Patient dead — 22 mo.
7	M	48	Renal carcinoma	3 mo.	February, 1951	Lobectomy (right middle lobe)	Patient dead — 26 mo.
11	F	47	Adenocarcinoma; colon.	1 yr.	October, 1952	Lobectomy (right upper lobe)	Patient dead — 17 mo.
					May, 1953	Lobectomy (left lower lobe)	
12	M	53	Fibrosarcoma; arm.	18 mo.	January, 1953	Lobectomy (right upper & middle lobes)	Patient dead — 24 mo.
					June, 1953	Local excision	
13	M	68	Renal carcinoma	13 yr.	October, 1953	Lobectomy (left lower lobe)	Patient dead — 19 mo.
14	M	60	Adenocarcinoma; colon.	16 mo.	March, 1953	Lobectomy (right upper lobe)	Patient dead — 9 mo.
15	F	50	Renal-cell carcinoma; fibrosarcoma; thyroid carcinoma.†	1st seen†	January, 1953	Lobectomy (right upper lobe)	Patient dead — 7 mo.
18	F	48	Melanocarcinoma; skin.	5 yr.	January, 1955	Lobectomy (right upper lobe)	Patient dead — 6 mo.
19	F	38	Epidermoid carcinoma; cervix.	6 yr.	October, 1955	Lobectomy (right lower lobe)	Patient dead — operative death
20	F	51	Epidermoid carcinoma — cervix†; adenocarcinoma — fundus.	10 mo.†	November, 1955	Pneumonectomy (left)	Patient dead — 1 mo.

*Case numbers indicate order in which patients seen & operated on.
†Primary tumor from which metastasis arose.

The multiplicity of pulmonary metastases deserves some consideration. Resection of both upper lobes for metastatic lesions secondary to neurogenic sarcoma has been reported by Alexander and Haight,[2] although these metastases did not coexist and the lobectomies were performed a year apart, with seven-year survival. In this connection, the term "solitary metastasis," as used by Effler and Blades[5] in the broad sense meaning that only one can be demonstrated, may have to be amended to fulfill the criterion that metastases be limited to the lung — admittedly a wishful thought in the majority of cases.

With a solitary metastasis so situated that only total pneumonectomy will suffice to remove it this operation should be performed, in my opinion, if pulmonary-function studies indicate that the procedure will be tolerated. Graham[6] doubts if this is a wise procedure because not enough experience has accumulated to indicate whether the advantage of a wide resection outweighs the danger of making the patient a pulmonary cripple. If adequate data on the functional reserve of the patient suggest that he can survive comfortably on one lung, in view of the desperate nature of these situations I have believed that pneumonectomy should be carried out. Total pneumonectomy has been performed on 3 such patients, 1 of whom (Case 2, Table 1) has now survived for over six years in comfort and is working; a similar case has been reported by Hood et al.[3] The second pneumonectomy (No. 16, Table 1) was performed for metastatic fibrosarcoma. The patient was alive and apparently well and working eighteen months later. The third patient (No. 20, Table 1) died only a month after operation.

Palliation

Under unusual circumstances, resection of metastatic pulmonary lesions may be undertaken to confer palliation without hope of cure. Such cases include the complications of hemorrhage and suppuration. Palliation was conferred on 1 patient (Case 10, Table 1) for at least a year after lobectomy for metastatic melanocarcinoma. She had been harassed by the expectoration of large amounts of blood and tarry melanotic pigment. She was lost to follow-up study after a year.

In the realm of conjecture is the amount of palliation that may be afforded patients who do not present severe pulmonary symptoms at the time the metastasis is discovered. Obviously, one can have no certain knowledge that because of such an operation the patient may be spared distressing symptoms.[3]

Material

This report is based upon 22 resections of pulmonary tissue performed on 20 patients with proved metastatic pulmonary disease (Table 1).* There were 2 wedge resections, 2 segmental resections, 15 lobectomies and 3 total pneumonectomies (Table 1). No conclusions can be drawn about survival time in relation to type of operation. As pointed out by others[3] it appears that lesser resections can be done for metastases in view of the fact that the pathways of extension in metastatic disease in the lung are less likely to be along the lymphatics than in primary neoplastic disease of the lung.

*I am indebted to Dr. Joseph P. Lynch for permission to report Cases 1, 4 and 7, Dr. Irving M. Madoff (Case 13), Dr. Lamar Soutter (Case 15) and Dr. George W. B. Starkey (Case 18). The remaining cases were operated upon by me or under my supervision.

In this series there were 17 carcinomas and 3 sarcomas (Table 2). One can draw no valid conclusions about survival on the basis of the type of tumor although, on theoretical grounds, the most malignant types should stand in the worst prognostic light. In this small series, as in others,[3] the sarcomas did as well as the carcinomas. The best results were in 2 patients

TABLE 2. *Types of Primary Tumor and Subsequent Course.*

TYPE OF TUMOR	SUBSEQUENT COURSE
Carcinoma (17 cases):	
Hypernephroma	4 (2 dead & 2 living & well)
Adenocarcinoma of uterus	2 (2 alive & well)
Adenocarcinoma of bladder	1 (alive & well)
Adenocarcinoma of colon	3 (2 dead & 1 alive with disease)
Adenocarcinoma of thyroid gland	2 (dead)
Melanocarcinoma of skin	1 (dead)
Melanocarcinoma of eye	1 (well after 12 mo. — lost to follow-up study)
Squamous-cell carcinoma of cervix	2 (1 operative death & 1 died of disease)
Adenocarcinoma of breast	1 (alive with disease)
Sarcoma (3 cases):	
Fibrosarcoma	2 (1 dead & 1 alive)
Leiomyosarcoma	1 (alive)

with adenocarcinoma of the fundus of the uterus (Cases 3 and 6), who survived for eighty and fifty-eight months respectively; 2 patients with hypernephroma (Cases 1 and 8), who survived for ninety-eight and fifty-two months respectively; 1 patient with adenocarcinoma of the bladder (Case 2), who survived for eighty-one months; and 1 patient with leiomyosarcoma of the uterus (Case 9) who survived for ten months.

In like manner, although it has been suggested that the time between the removal of the primary lesion and the appearance of the pulmonary metastasis bears a direct relation to the survival after resection of the pulmonary lesion, this does not appear to have been so in this series. However, of the 10 patients alive, 7 did not show the metastatic lesions until four or more years after resection of the primary tumor. This is in contrast to only 3 of the 10 who died.

There were 5 patients under the age of fifty. Three of these died one, six and twenty-six months after pulmonary resection. One is alive with recurrence after seventy-one months, and 1 is alive and well eighty-one months after removal of the metastasis (Table 1).

There was 1 operative death (Case 19), in a thirty-eight-year-old woman who suffered lower-nephron nephrosis as the result of a transfusion reaction on the basis of disseminated carcinomatosis involving the bone marrow.

The number of patients in this series is too small

for conclusions of statistical significance to be drawn. Four patients have survived for more than five years, 1 with disease. It is of interest that of 41 patients followed by the Mayo Clinic[3] 30, or 73.2 per cent, survived for more than a year, and in the present series, 15, or seventy-five per cent, survived for a year or more.

Summary and Conclusions

The current attitude in the treatment of metastatic neoplastic deposits in the lungs is discussed.

It is noted that suspected metastatic lesions may in fact be primary tumors and possibly benign.

Criteria for selection of cases for operation are stated.

The results of 22 pulmonary resections for metastatic lesions in 20 patients are reviewed.

Although it is agreed that no hard-and-fast criteria can as yet be established for operations in metastatic pulmonary disease, the results of this series and others appear to justify the continuation of pulmonary resection in selected cases for metastatic neoplastic pulmonary disease. It seems reasonable to state that, in a patient whose primary lesion has apparently been successfully treated, who has a solitary metastasis so located that it can be resected and who has no other demonstrable extrapulmonary metastases, the pulmonary lesion should be seriously considered for resection.

References

1. Barney, J. J. D. Twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. *J. Urol.* **52**: 406, 1944.
2. Alexander, J., and Haight, C. Pulmonary resection for solitary metastatic sarcomas and carcinomas. *Surg., Gynec. & Obst.* **85**: 129-146, 1947.
3. Hood, R. T., Jr., McBurney, R. P., and Clagett, O. T. Metastatic malignant lesions of lungs treated by pulmonary resection: report of 43 cases. *J. Thoracic Surg.* **30**:81-89, 1955.
4. Minor, G. R. Clinical and radiological study of metastatic pulmonary neoplasms. *J. Thoracic Surg.* **20**:34-42, 1950.
5. Effler, D. B., and Blades, B. Surgical treatment of solitary lung metastasis. *J. Thoracic Surg.* **17**:27-37, 1948.
6. *The 1952 Year Book of General Surgery (June 1951-May 1952).* Edited by E. A. Graham. 670 pp. Chicago: Yearbook Publishers, 1952. P. 210.
7. Cahan, W. G., Butler, F. S., Watson, W. L., and Pool, J. L. Multiple cancers: primary in lung and other sites. *J. Thoracic Surg.* **20**:335-348, 1950.

IMPROVEMENTS IN CANCER SURVIVAL RATES

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THE Cancer Control Program in Connecticut is a co-operative venture conducted by four organizations: the Connecticut State Medical Society; the Association of Connecticut Tumor Clinics; the Connecticut Division of the American Cancer Society; and the Connecticut State Department of Health. The efforts of these four groups are sponsored by a cancer co-ordinating committee of nine members appointed by the Connecticut State Medical Society. There are three mandatory appointments to this committee: the president of the Connecticut Cancer Society; the chairman of the Association of Connecticut Tumor Clinics; and a representative of the Connecticut State Department of Health. The other six are members-at-large. The Association of Connecticut Tumor Clinics is an autonomous organization made up of representatives of all the 27 tumor clinics in the State.

History of the Connecticut Cancer-Control Program

This program was initiated in 1933, when the Connecticut State Medical Society voted to authorize the appointment of a tumor study committee. In 1935 the Governor signed a bill sponsored by the Medical Society and the State Department of Health that, in December of that year, led to the organization of a division of cancer research within the Department. The Association of Connecticut Tumor Clinics was formed in the same year to represent the tumor clinics then in existence and those that might be organized later. In 1941 the Connecticut Branch of the American Society for the Control of Cancer was formed. These organizations are still in existence but with changes in name, with the exception of the Association of Connecticut Tumor Clinics, which has retained its original designation. The Tumor Study Committee became the Cancer Coordinating Committee; the Division of Cancer Research became the Division of Cancer and Other Chronic Diseases; and the Connecticut Branch of the American Society for the Control of Cancer became the Connecticut Division of the American Cancer Society.

Each unit has its place in the program, the representatives of the Medical Society and the Association of Connecticut Tumor Clinics governing the clinical aspects of the work, the Connecticut Division of the American Cancer Society directing its efforts toward lay and professional education, the promotion of research and service to patients, and the Division of Cancer and Other Chronic Diseases in the State Department of Health maintaining the Cancer Rec-

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ord Register, collecting and analyzing data, subsidizing clinics and cosponsoring professional education.

The fact that for nearly twenty years the four organizations concerned have been able to co-operate and to co-ordinate their efforts demonstrates conclusively that diverse groups can work together to formulate and conduct an effective cancer-control program.

Analysis of Survival Experience

The Connecticut Cancer Record Register provides an excellent opportunity to evaluate therapy in terms of survival. It is a unique source of information in that it contains data on a large series of patients with cancer diagnosed during an extended period, and drawn from a known population base. Thus, it is possible to study the survival experience of all patients known to have cancer seen in the hospitals of a large community, rather than the experience of patients seen in one institution, or a selected series of patients exposed to a specific therapeutic course. The register provides an opportunity to measure the trend in survival rates and thus to determine how much progress, if any, has been made in the management of these patients. Furthermore, the number of cases available for analysis is large enough to permit evaluation of the interrelated influence on survival of such factors as age, sex, primary site, stage at diagnosis and method of treatment.

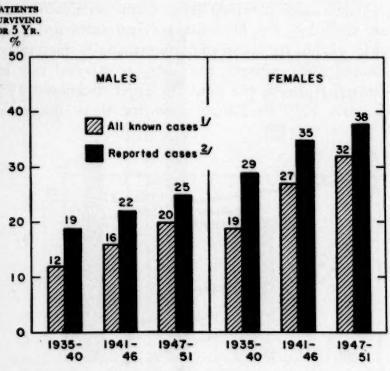

Figure 1. *Percentage of Patients Surviving for Five Years after Diagnosis of Cancer (Connecticut Residents during 1935-40, 1941-46 and 1947-51).*

1 includes cases obtained from death certificates only, in which patients were assumed to have died within five years of diagnosis.

2 includes cases reported by hospitals.

This report deals with the survival experience of 75,494 cases of cancer among residents of Connecticut diagnosed during the seventeen-year period 1935-1951, and is based on follow-up information through December 31, 1951. To facilitate analysis of the trend in survival rates, the seventeen-year period has been divided into three parts: 1935-1940, 1941-1946 and 1947-1951. Since primary interest here is in a comparison of the survival experience of patients with diagnoses made in each of the three time periods, the discussion is largely limited to five-year survival rates. End results over a longer follow-up period will be reported in a future paper.

Table 1. *Cases of Cancer Diagnosed in Connecticut Residents during 1935-1940, 1941-1946 and 1947-1951 According to Source of Information.*

Period	Total No. of Cases Diagnosed	Cases Reported by Hospitals		Diagnoses Obtained from Death Certificates	
		Number	Percentage	Number	Percentage
1935-1940	21,712	13,975	64	7,737	36
1941-1946	26,223	20,106	77	6,117	23
1947-1951	27,559	22,827	83	4,732	17
Totals (1935-1951)	75,494	56,908	—	18,586	—
Averages			75		25

The methodology employed in computing these rates is discussed in a monograph containing a detailed statistical analysis of the data in the Connecticut Cancer Register.[1] The procedures are in general agreement with the recommendations of the Joint Committee on Reporting Cancer End Results*:

> All cases diagnosed as malignant neoplasm are included in the analysis — untreated† as well as treated, and those with clinical diagnoses only, as well as microscopically confirmed cases.
>
> The effect of the clinically diagnosed cases on the computed survival rates is evaluated.
>
> Survival is measured from date of first diagnosis. Although it is theoretically desirable to measure survival from date of onset, this information is generally unreliable.
>
> The number of untraced patients was small — less than 5 per cent — for five-year follow-up study.
>
> This report is limited to survival rates. Information on disease status on selected anniversaries will be included in a subsequent report.
>
> Only newly diagnosed cases are dealt with here. A special report is contemplated on the survival experience of recurrent cases.
>
> The procedures in this analysis differed from the committee recommendations in that the analysis was not restricted to cases with an elapsed

*This group is composed of representatives of the American College of Surgeons, College of American Pathologists, American College of Radiology, American Cancer Society and United States Public Health Service.[2]

†A fourth of the patients with this diagnosis during the seventeen-year period were not treated definitively.

duration of at least five years. Standard actuarial procedures were used to account for the experience of cases diagnosed within five years of the study cut-off date.

TABLE 2. *Patients Surviving for One and Five Years after Diagnosis, According to Sex (Connecticut Residents, 1935-1940, 1941-1946 and 1947-1951).**

GROUP	MALE PATIENTS			FEMALE PATIENTS		
	1935-1940	1941-1946	1947-1951	1935-1940	1941-1946	1947-1951
	%	%	%	%	%	%
Patients surviving for 1 yr.:						
Microscopically confirmed cases	47	50	54	63	68	69
Cases with clinical diagnosis only	23	28	31	29	30	33
Patients surviving for 5 yr.:						
Microscopically confirmed cases	24	26	27	34	40	41
Cases with clinical diagnosis only	9	12	12	11	14	14

*Includes only microscopically confirmed & clinically diagnosed cases, cases obtained from death certificates only being excluded.

Three out of every 4 cases in the register were reported by the hospitals co-operating in the program. The only information available on the remaining group of cases was obtained from death certificates (Table 1). As the case-reporting program developed, the proportion of cases reported by hospitals increased. Of the cases diagnosed during the period 1935-1940, 64 per cent were reported by hospitals co-operating in the program. This figure rose to 83 per cent during the most recent period, 1947-1951. A substantial part of the increase can be attributed to more complete reporting on the part of the hospitals, but some of it probably reflects greater use of hospital facilities for diagnosis and treatment through the establishment of additional tumor clinics in general hospitals throughout the State.

The diagnosis was microscopically confirmed in 80 per cent of the 56,908 cases reported by hospitals. This figure has risen from 73 per cent for cases diagnosed in 1935 through 1940 to 86 per cent for those diagnosed during the period 1947-1951. The increase in the use of microscopical technics for confirming diagnoses may be interpreted as reflecting improved medical practice in the management of cancer.

Survival Rates for All Forms of Cancer

The trend in five-year survival rates indicates that the outlook for diagnosed cases is improving. Among cases reported by hospitals, 19 per cent of male patients with diagnoses made during the period 1935-1940 were alive five years later. The corresponding five-year survival rate for cases in males diagnosed in 1947 through 1951 was 25 per cent. Among female patients, the five-year survival rate was 29 per cent for cases diagnosed in 1935 through 1940 and 38 per cent for those diagnosed in 1947 through 1951.

When cases obtained from death certificates only are included, the five-year survival rates are lower (Fig. 1), but the trend remains essentially unchanged. Among male patients, the five-year survival rate increased from 12 per cent for cases diagnosed 1935 through 1940 to 20 per cent for those diagnosed 1947 through 1951. Among female patients, the corresponding figures are 19 and 32 per cent.

The survival rates based on all known cases of cancer, including those obtained solely from death certificates, are of interest because they provide insight into the survival picture for all persons in whom cancer develops in a community. However, there are several reasons for giving primary interest to the

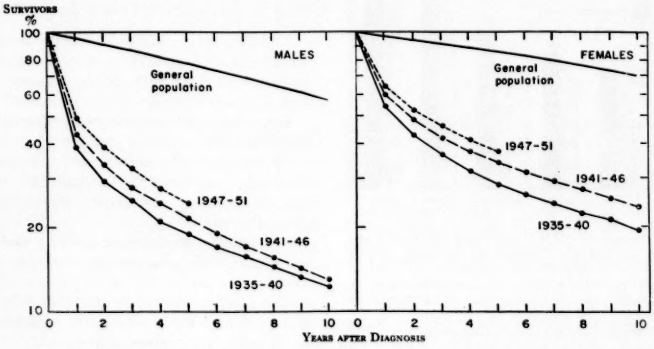

FIGURE 2. *Percentage of Patients Surviving up to Ten Years after Diagnosis, According to Sex.*

survival experience of cases reported to the register by hospitals:

The actual date of diagnosis is known.

A substantial proportion of cases obtained from death certificates probably represent cases in which the physician signing the death certificate attended the patient only at death.

We are interested in survival rates as a measure of success in case management.

Consequently, the remainder of this discussion is restricted to the survival experience in the 56,908 cases reported by hospitals.

The survival rates in this report are based on all reported cases of cancer, whether or not the diagnosis was confirmed by microscopical examination of tissue. Does the inclusion of cases with only a clinical diagnosis, 20 per cent of the total, tend to inflate or depress survival rates for cancer? The data in Table 2 provide an answer to the question.

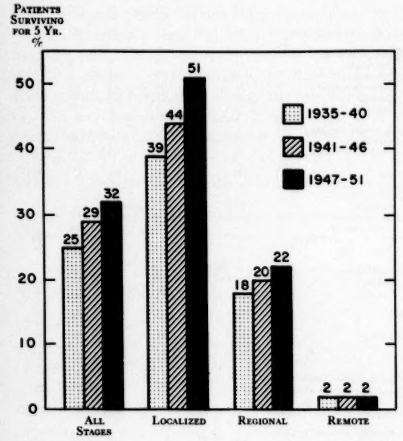

FIGURE 3. *Five-Year Survival Rates, According to Stage at Diagnosis.*
Cases obtained from death certificates only are excluded. Cancers of the lymphatic and hematopoietic systems are included under "all stages."

In each of the three time periods the survival rates for cases with clinical diagnoses only were considerably lower than those for microscopically confirmed cases. Since patients with clinical diagnoses only are generally older than those with confirmed cases, one would expect fewer of them to survive for five years. However, over a period of a year, "normal" mortality should not be markedly different. Table 2 indicates that approximately twice as many patients with confirmed as those with clinically diagnosed cases survived for one year. Thus, it is obvious that irrespective of the influence of age at diagnosis, the inclusion of the clinically diagnosed cases tends to depress rather than to inflate the survival rates for cancer. The low rates for the clinically diagnosed cases suggest that this group is probably made up in large part of patients for whom biopsy or any major surgical procedure was considered either unnecessary or medically inadvisable. The observed survival rates do not support the belief that patients with cancer diagnosed clinically have a higher survival rate, because there is inadequate proof that they have cancer.

TABLE 3. *Distribution, According to Stage at Diagnosis.**

STAGE	MALE PATIENTS			FEMALE PATIENTS		
	1935-1940	1941-1946	1947-1951	1935-1940	1941-1946	1947-1951
	%	%	%	%	%	%
Localized	58	58	56	52	56	54
Regional involvement	21	22	26	30	29	32
Remote metastases	21	20	18	18	15	14
Totals	100	100	100	100	100	100

*Excludes cases obtained from death certificates only & reported cases primary in hematopoietic and lymphatic systems.

Survival Pattern

The percentage of patients alive five years after diagnosis reflects cumulative mortality during a five-year period. Is the mortality rate constant during this period, does it increase with time, or does it taper off? Has the pattern changed during the seventeen-year period under study?

The percentages of patients alive at ten successive annual anniversaries after diagnosis are shown in Figure 2. (For cases diagnosed from 1947 through 1951 only five years of experience can be shown at this time.) A semilogarithmic scale has been used, because change in the rate of depletion (mortality) of the group being followed is of primary interest here.

This figure reveals that the mortality rate among patients with cancer is high during the first year after diagnosis and then tapers off. This was true for male and female patients with cases diagnosed in each of the three periods. To provide a frame of reference, Figure 2 also indicates the expected survival experience of a group of persons drawn from the general population and with an age distribution similar to that of the cancer population.* After about five years, the curves for both male and female patients with cancer become more nearly parallel to the curves for the general population. This means that the mortality risk for patients alive five years after diagnosis is not much greater that that for the population at large.

*The effect of age at diagnosis on the expected and observed survival experience of cancer patients has been reported on by Pollack.[3]

The percentage of patients alive one year after diagnosis was substantially different for cases diagnosed in each of the three periods, as shown by differences in the levels of the plotted points. However,

TABLE 4. *Patients Treated by Surgery* during the First Course of Medical Care, According to Stage at Diagnosis.†*

STAGE	PERIOD OF DIAGNOSIS		
	1935-1940	1941-1946	1947-1951
	%	%	%
Localized	58	63	75
Regional involvement	60	64	70
Remote metastases	30	33	38
Totals‡	50	55	63

*Includes other methods of treatment combined with surgery.
†Excludes cases obtained from death certificates only.
‡Includes cancers of lymphatic & hematopoietic system.

from one year on, among both males and females, the survival curves for the three groups are parallel. Thus, the differences in the levels of the curves beyond the first year are essentially carry-overs of the differences in the one-year survival percentages.*

Influence of Stage at Diagnosis and Therapy

Though stage at diagnosis is a controlling factor in prognosis, the observed improvement in the five-year survival rates, from date of diagnosis, among these patients appears to be due to more effective utilization of available therapeutic technics. As indicated in Figure 3, there has been a great improvement in the five-year survival rate for cases of cancer diagnosed while localized at the site of origin (from 39 per cent for cases diagnosed from 1935 through 1940 to 51 per cent for those diagnosed from 1947 through 1951), and a notable improvement in the survival rate for cases with regional involvement at diagnosis (from 18 to 22 per cent). As might have been expected, the survival rate for cases diagnosed after remote metastases have occurred has remained at a very low level — 2 per cent. The data in Table 3 indicate that in general the observed trend was not due to an increase in the proportion of cases discovered early, with the exception of certain accessible sites. In both male and female patients, there has been little change in the distribution of newly diagnosed cases by stage. Since the higher survival rates for localized and regional cases were accompanied by higher rates for all stages combined, the increase in survival rates by stage cannot be attributed to changes in the classification of cancer by stage. The foregoing considerations lead to the conclusion that therapy rather than a shift in stage at diagnosis was primarily responsible for the improved survival experience of patients with cancer in Connecticut.

*The stability of the mortality rates after the first year indicates that although five-year follow-up study on cases diagnosed from 1947 through 1951 was incomplete as of December 31, 1951, the computed five-year survival rates for this group may be accepted with a high degree of confidence.

Surgical intervention was employed in 50 per cent of cases diagnosed between 1935 and 1940. The corresponding figures for the next two periods were 55 per cent in 1941 through 1946 and 63 per cent in 1947 through 1951. When the cases are classified by stage at diagnosis, the shift is found to be similar for all three stages (Table 4). The increased use of surgical intervention in the treatment of cancer was accompanied by an improvement in survival among surgically treated cases. For example, the one-year survival rate for cases treated solely by surgery increased from 60 to 72 per cent, from the first to the third period; the corresponding five-year survival rates were 34 and 43 per cent.

TABLE 5. *Patients Surviving for Five Years after Diagnosis, According to Sex and Primary Site.**

PRIMARY SITE	MALE PATIENTS			FEMALE PATIENTS		
	1935-1940	1941-1946	1947-1951	1935-1940	1941-1946	1947-1951
	%	%	%	%	%	%
All sites	19	22	25(3)	29	35	38(3)
Buccal cavity & pharynx	36	35	35	34	43	44
Digestive system:						
Esophagus	0	0	2	5	2	8
Stomach	4	7	5	4	3	7
Large intestine	12	17	24(3)	14	24	33(3)
Rectum	10	15	21(3)	13	22	31(3)
Pancreas	1	1	†	2	2	†
Respiratory system:						
Larynx	25	27	37(1)	†	†	†
Lung & bronchus	0	2	3	4	3	8
Breast	36	27	51	41	47	46(1)
Genital organs:						
Prostate	12	22	21(2)	—	—	—
Cervix uteri	—	—	—	35	43	53(3)
Corpus uteri	—	—	—	48	59	62(2)
Uterus, unspecified	—	—	—	37	45	50(2)
Ovary	—	—	—	22	22	24
Urinary system:						
Kidney	13	22	27(1)	16	23	16
Bladder	23	24	28	22	23	36(1)
Skin	61	65	67	66	73	68
Soft tissue	49	38	48	48	49	52
Bone	30	19	28	27	25	32
Brain & other parts of central nervous system	19	18	20	19	23	25
Endocrine glands, NEC‡	9	23	†	26	37	54(2)
Lymphatic system, generalized	19	21	27	16	23	22
Hematopoietic system	6	6	12(1)	4	7	11

*Numbers in parentheses indicate probability that observed differences between survival rates for cases diagnosed in 1935-40 & 1947-51 could have occurred by chance: (1), less than 5 in 100; (2), less than 1 in 100; (3), less than 1 in 1000. Statistical significance tested by Greenwood's[4] formula, which takes into account fact that some cases not observed for full 5 yr.
†Insufficient number of cases available for follow-up study.
‡Excludes pancreas, ovary & testis.

The percentage of cases treated with radiation, alone or in combination with surgery or chemotherapy, or both, decreased from 32 to 22 per cent, from the first to the third period. Survival rates for cases treated by radiation increased, but to a lesser extent than those for surgically treated cases. For example, for cases treated solely by radiation the one-year survival rate rose from 59 to 63 per cent, from the

first to the third period; the five-year survival rate increased from 28 to 34 per cent.

The relation of the patient's condition and the type and extent of therapy to prognosis needs to be studied. A more detailed discussion of cancer therapy and its relation to survival will be included in a forthcoming paper.

Survival Rates by Primary Site

Information on survival by primary site is given in Table 5. It is evident that the improved outlook for these patients as a group does not apply to all forms of cancer. The data collected in the Connecticut Cancer Record Register do not point to a hopeful prognosis, at present, for persons with cancer of the stomach, lung, esophagus, ovary, bone and brain. The prognosis for the first three groups is particularly poor. On the basis of the Connecticut experience, fewer than 10 per cent of patients with cancer of the stomach, lung, and esophagus may be expected to live for five years.

In sharp contrast to the experience with these forms of cancer, there has been a marked increase in five-year survival rates for cancer of the large intestine, rectum, cervix, corpus, prostate and endocrine glands. The relative change in five-year survival rates for cases diagnosed in 1947 through 1951 as compared with those diagnosed in 1935 through 1940 is shown in Table 6. In addition to the forms of cancer mentioned above, noteworthy improvement in survival was observed for cancer of the larynx, breast, kidney, bladder and hematopoietic system. However, the improvement in survival for persons with cancers primary in these sites was statistically less significant than that for the previously listed sites.

Examination of the distribution of cases by stage at diagnosis indicated that more effective utilization of available therapeutic technics, especially surgery, was apparently a more important factor than earlier case finding in increasing the proportion of patients alive five years after diagnosis. There was no increase in the proportion of cases diagnosed while localized for cancers of the large intestine, rectum, corpus, prostate, kidney, bladder and hematopoietic system. Earlier case finding was a contributory factor in increasing the proportion of five-year survivors for cancer of the cervix, breast, larynx and endocrine glands.

TABLE 6. *Change in Five-Year Survival Rates, 1947-51 and 1935-40.*

PRIMARY SITE	INCREASE	
	MALE PATIENTS	FEMALE PATIENTS
	%	%
Large intestine	100	136
Rectum	110	138
Cervix uteri	—	51
Corpus uteri	—	29
Prostate	75	—
Endocrine glands, NEC	*	108

*Insufficient number of cases available for follow-up study to yield reliable survival rate for cases diagnosed in 1947-51.

For further evaluation of the apparent influence of progress in therapy on survival, survival rates by stage at diagnosis were computed for cases diagnosed in each of the three periods. This was possible only for sites with a sufficiently large number of cases to yield reliable survival rates, by stage at diagnosis. The results of this analysis are summarized in Table 7. There was definite improvement in survival for pa-

TABLE 7. *Patients Surviving for Five Years after Diagnosis, According to Selected Primary Sites by Stage of Disease at Diagnosis.**

PRIMARY SITE	ALL STAGES			LOCALIZED LESIONS			REGIONAL INVOLVEMENT			REMOTE METASTASES
	1935-1940	1941-1946	1947-1951	1935-1940	1941-1946	1947-1951	1935-1940	1941-1946	1947-1951	1935-1951†
All sites	25	29	32	39	44	51	18	20	22	2
Stomach	4	6	6	7	13	13	4	2	5	‡
Large intestine	13	21	29	24	34	48	10	19	30	1
Rectum	12	18	25	17	27	43	9	15	25	1
Bronchus & lung	1	2	4	§	4	6	§	2	6	0
Breast	41	47	46	65	65	66	31	38	37	2
Prostate	12	22	21	18	26	25	§	§	§	7
Cervix uteri	35	43	53	45	51	65	26	32	33	§
Corpus uteri	48	59	62	56	66	69	§	§	§	§
Bladder	23	24	31	28	29	40	§	§	§	§

*Male & female patients combined.
†5-yr. survival rates for persons found to have cancer after remote metastases had occurred did not change during 17-yr. period under study.
‡Less than 0.5 per cent.
§Insufficient number of cases available for follow-up study.

tients with localized or regional cancers of the large intestine, rectum and cervix. Five-year survival increased for localized cancers of the prostate, corpus and bladder. There were not enough regional cases primary in these sites to yield reliable rates.

The trend in survival, by stage at diagnosis, was unique for cancer of the breast. Whereas the percentage of five-year survivors increased for cases with regional involvement at diagnosis, there was no change for localized cancers of the breast, the rate remaining stabilized at 65 to 66 per cent.

As indicated previously, the survival outlook for patients with cancers primary in the stomach, lung, esophagus, ovary, bone and brain has remained poor. These parts of the body are relatively inaccessible to direct examination, and the tests available for diagnosis of cancers at these sites are generally cumbersome and difficult to interpret. A relatively small proportion of cancers originating in the stomach, lung and ovary are diagnosed in an early stage of development. At present, for cancers of the lung, stomach, esophagus and brain, prognosis is poor even in cases considered to be localized at the time of diagnosis. Further research into diagnostic methods to uncover the silent, hidden cancers, as well as additional advances in therapeutic technics, is apparently required if better control of cancer is to be achieved.

Discussion

This summary of the survival experience of patients with cancer in Connecticut can serve as a base line for comparison with the experience of selected series of patients assembled by individual hospitals and physicians. When one is making comparisons, however, it should be borne in mind that the data in this report include all diagnosed cases, untreated as well as treated.

Summary

The Connecticut Cancer Record Register has information on 75,494 cancer cases diagnosed from 1935 through 1951. Follow-up information reveals that the outlook for survival is improving for some forms of cancer. Marked increases in five-year survival rates were observed for patients with cancers of the large intestine, rectum, cervix, corpus, prostate and endocrine glands. Both earlier case finding and more effective utilization of available therapeutic technics apparently were factors in increasing the proportion of cancer patients alive five years after diagnosis. Effective use of technics has had a more measurable effect in recent years. Further increase in survival must be predicated on research for better diagnostic and therapeutic methods.

References

1. Connecticut State Department of Health. *Cancer in Connecticut, 1935-1951.* (in press).
2. Joint Committee on Reporting Cancer End Results. Standardized method for reporting cancer and end results. *CA* 3:80-84, 1953.
3. Pollack, E. S. Effect of age and site on life expectancy of cancer patients. *Connecticut Health Bull.* 68:193-200, 1954.
4. Greenwood, M. *Report on the Natural Duration of Cancer. (Reports on Public Health and Medical Subjects* No. 33.) 26 pp. London: His Majesty's Stationery Office, 1926.

ACUTE ADRENAL INSUFFICIENCY AND ACUTE MYOCARDIAL INFARCTION*

Simultaneous Occurrence Associated with Marked Eosinophilia and Recovery

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Boston

ACUTE adrenal insufficiency has not been previously described in association with acute myocardial infarction. Review of the available literature shows that the most recent report is that of Appelman,[1] whose patient with Addison's disease had evidence of an old myocardial infarct at the time diagnosis was made. It is the purpose of this communication to present observations on a case of acute myocardial infarction and acute adrenal insufficiency occurring simultaneously and associated with marked eosinophilia.

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Case Report

A 60-year-old male schoolteacher was admitted to the Surgical Service of the Veterans Administration Hospital, White River Junction, Vermont, on November 15, 1954, complaining of pain in the right great toe. For 1½ weeks he had had constant aching and darkening in color of the toe. Except for moderate dyspnea on exertion secondary to pulmonary emphysema he had been in excellent health. Dietary habits were good, with no history of uncooked-pork ingestion. Thirty years previously he had undergone a tonsillectomy and appendectomy without difficulty.

His father had died at the age of sixty of "heart trouble." A daughter had been admitted to a sanatorium 6 months previously with questionable tuberculosis, but no active disease had been found.

Physical examination showed an intelligent and alert though somewhat tired man who was in pain from his right great toe. He was adequately nourished and hydrated. There was a well healed appendectomy scar, and there was no evidence of abnormal pigmentation. The retinal arterioles were narrowed, and the chest and lungs revealed mild em-

physema. The heart was normal. Pedal pulses were diminished to absent. The distal two thirds of the right great toe was dark blue and cool.

The temperature was 98°F., and the pulse 74. The blood pressure was 130/72.

An electrocardiogram was normal; x-ray study of the chest demonstrated pulmonary emphysema and calcification of the aortic arch. Examination of the blood (Table 1), a serologic test for syphilis and urinalysis were negative, but the erythrocyte sedimentation rate was 87 mm. per hour. The initial diagnoses were arteriosclerosis obliterans, with gangrene of the right foot, and pulmonary emphysema.

On November 18 a right-sided lumbar sympathectomy was performed, and under thiopental (Pentothal), succinylcholine and nitrous oxide anesthesia the patient did well. Briefly during the procedure the blood pressure fell to 85/74 but rose to 130/80 at the end, 3 hours and 15 minutes later. The next day the blood pressure was 100/60, and he was eating well. He made good progress until 7 days later, when he complained to the nurse of substernal discomfort and was noted to be sweating. When later seen by a doctor he denied chest pain and described only indigestion and vague aching in the left upper quadrant. During the next 4 days he had 2 similar episodes, but there were no abnormal physical findings and the blood pressure remained 132/70. After this he had no further discomfort but occasionally appeared mentally depressed. His appetite was decreased, he periodically complained of nausea, and he slept much of the time. From December 1 to 8, the blood pressure ranged from 100/60 to 108/70. During this period the white-cell count was normal, with 1 per cent eosinophils. On December 10, 22 days after operation, the white-cell count was 10,550, with 33 per cent segmented neutrophils, 4 per cent band forms, 3 per cent monocytes, 48 per cent lymphocytes and 12 per cent eosinophils (Table 1). One hour later, while using the bedside commode, the patient complained of severe pain in the lower left anterior part of the chest, sweating and weakness. The blood pressure was 86 systolic, and the heart sounds could not be heard. An electrocardiogram revealed marked elevation of the ST segment in Leads 2, 3 and aVF, with reciprocal depression in Leads 1, V_1 through V_6 and aVL. These changes were interpreted as consistent with acute posterior myocardial infarction (Fig. 1).

On transfer to the Medical Service, the patient appeared gravely ill, but there was no evidence of shock or cardiac decompensation. There was a diastolic gallop at the cardiac apex; otherwise, physical examination was unchanged. He was treated with bed rest, oxygen and Dicumarol. For the next 4 days the blood pressure ranged between 68/40 and 84/60 although neither clinical shock nor cardiac failure appeared, and he remained alert and took soft food and liquids. On the 5th day after the infarction he exhibited marked disorientation and mental confusion and was dehydrated; the nonprotein nitrogen was 46 mg. per 100 ml. The mental confusion worsened during the next 2 days while glucose and water were being given intravenously. Eight days after the infarction the serum total base was 131.5 milliequiv., the chloride 83.0 milliequiv., and the bicarbonate 29.5 milliequiv. per liter[2,3]; 155 milliequiv. of sodium and 40 milliequiv. of potassium were given intravenously. On the following day when the serum total base was 128.0 milliequiv. per liter, 310 milliequiv. of sodium was given, partially as 5 per cent saline solution. On the next day the serum sodium was 125 milliequiv., the potassium 4.7 milliequiv., and the chloride 92.4 milliequiv. per liter. The patient's mental status cleared markedly, and he began to take food and liquid.

TABLE 1. *Summary of Laboratory Data.*

Time of Examination	Sodium	Potassium	Nonprotein Nitrogen	White-Cell Count	Eosinophils	Hemoglobin	Erythrocyte Sedimentation Rate
	milliequiv./liter	*milliequiv./liter*	*mg./100 ml.*		%	*gm./100 ml.*	*mm./hr.*
On admission	—	—	—	9,400	2	13.4	87
Day of infarction	—	—	—	10,550	12	13.1	85
8 days after infarction	118.5*	—	46	16,150	30	—	119
10 days after infarction†	125.0	4.7	25	10,050	15	—	—
18 days after infarction	134.0	5.3	35	11,800	4	9.4	100
30 days after infarction	144.5	5.2	—	9,850	15	10.6	—
60 days after infarction	—	—	32	—	—	—	—
105 days after infarction‡	143.8	4.8	—	10,700	2	13.9	—
165 days after infarction	141.8	4.4	—	9,300	5	12.2	24

*Estimated from total base.
†Steroid therapy begun 12 days after infarction.
‡At discharge.

During the 8 preceding days the white-cell count had risen from 10,500, with 12 per cent eosinophils, to 16,150, with 30 per cent eosinophils, representing an estimated total eosinophil count of over 4000 (Table 1). To verify the suspected diagnosis of acute adrenal insufficiency an adrenal stimulating test was performed.[4-6] On December 21 the fasting total eosinophil count, determined according to the method of Thorn et al.,[7] was 518 per cubic millimeter; 40 units of ACTH gel (highly purified) was given intramuscularly. Eight hours later the eosinophil count was 343 per cubic millimeter, a 33 per cent fall. On the next day, 80 units of ACTH gel was given in the morning, and 8 hours later the eosinophil count was 775 per cubic millimeter, a 50 per cent rise. Twenty-four-hour urinary 17-ketosteroid excretion[8] on the 2 days before the test was 4.1 mg. and 3.8 mg. respectively. On the 2 days of stimulation the 24-hour urinary 17-ketosteroid excretion was 3.8 mg. and 4.7 mg. respectively (Fig 2).

It was believed that this represented a lack of adrenocortical response to ACTH and confirmed the diagnosis of adrenal insufficiency. In a series of normal subjects Thorn and his associates[4-6,9] have found a fall of 85 per cent or more in circulating eosinophils and an average rise of 8.7 mg. in 24-hour urinary 17-ketosteroid excretion after 2 days of 8-hour infusion of ACTH. Similar changes were observed after intramuscular administration of ACTH gel. Changes in patients with Addison's disease were considerably less.

Cortisone, 75 mg. a day, was started on December 22, and gradually, after 7 days, the dose was reduced to 25 mg. a day. Later, desoxycorticosterone acetate, 1 mg. a day, was added. On December 28, the patient experienced a prolonged bout of ventricular tachycardia. This responded to quinidine, and thereafter he gradually improved. The serum sodium rose to normal, as did the blood pressure, and the nonprotein nitrogen fell to 32 mg. per 100 ml. Appetite, mental alertness and general sense of well-being improved

soon after cortisone was started. During the episode of ventricular tachycardia mild cardiac failure did appear, but at no other time was there evidence of failure despite salt, cortisone and DOCA administration. Electrocardiograms showed progressive changes of a healing transmural posterior myocardial infarct, with inversion of the T wave and the appearance of a Q wave in Lead aVF. The PR interval, measured in Lead 2, increased after the infarction to 0.24 second, later returning to 0.16 second when the patient was receiving cortisone (Fig. 1).

thoracic ratio at the time of admission and at discharge showed no change, but because of the patient's precarious condition, a standard film was not taken during the period of acute adrenal insufficiency.

Beginning on January 30, while he was receiving 25 mg. of cortisone a day, 80 units of ACTH gel was given intramuscularly each day for 7 days. The control 24-hour urinary 17-ketosteroid excretion was 4.7 mg. On the 5th, 6th and 7th days of ACTH administration the 17-ketosteroid excretion was 3.3 mg., 6.6 mg. and 8.0 mg. respectively.

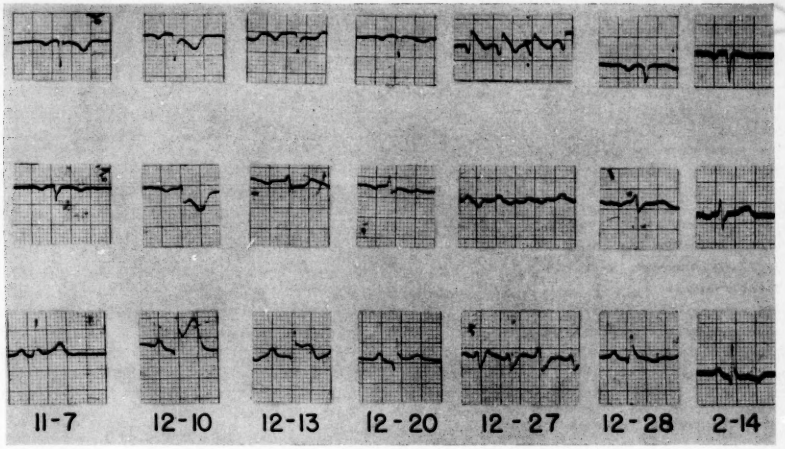

FIGURE 1. *Unipolar Limb-Lead Electrocardiograms.*
11-7-54: PR interval of 0.18 second (on admission) — normal tracing.
12-10-54: PR interval of 0.18 second — acute posterior myocardial infarction.
12-13-54: PR interval of 0.24 second — no treatment for adrenal failure.
12-20-54: PR interval of 0.20 second — saline solution intravenously for two days.
12-27-54: ventricular tachycardia.
12-28-54: PR interval of 0.18 second — patient on cortisone and quinidine.
2-14-55: PR interval of 0.16 second — old posterior myocardial infarction.

Between the 16th and 18th days after the myocardial infarction definite brown pigmentation appeared in the suture scars and on adhesive-tape areas around the fresh sympathectomy scar. This pigmentation did not recede with the administration of cortisone during the period of observation, and no other visible pigmentation appeared. Two months after the infarction the white-cell count was 9850, with 15 per cent eosinophils. The hemoglobin, which was 13.2 gm. per 100 ml. on the day of infarction, fell to 9.4 gm. per 100 ml. after hydration, salt replacement and steroid administration. This returned to normal over the next 2 months (Table 1).

On January 14, 1955, the patient successfully underwent a transmetatarsal amputation of the right foot.

Before discharge a number of procedures were carried out to elucidate the problem further. Numerous stool specimens were negative for blood, ova and parasites. Pathological examination of the amputated right foot revealed gangrene of the great toe, arterial thrombosis and obliteration of smaller vessels of the foot. There was no evidence of polyarteritis nodosa, and the cause of the obliteration of the blood vessels was not apparent. Smears and cultures of sputum for acid-fast bacilli were negative. No eosinophils were seen on the smear. A 2d-strength tuberculin test was positive. X-ray study of the abdomen revealed no abnormal calcification. Comparison of the heart size by cardio-

The patient was discharged on April 11 on 37.5 mg. of cortisone a day. At this time the white-cell and fasting eosinophil counts were normal.

On follow-up examination on May 26 the weight had increased from 68.5 to 73.0 kg. (151 to 161 pounds). The patient felt well, and the blood pressure was 122/80. The serum sodium was 141.8 milliequiv. per liter, and the white-cell count was 9300, with 5 per cent eosinophils.

DISCUSSION

The simultaneous occurrence of acute myocardial infarction and acute adrenal insufficiency has not been previously reported. Thorn[10] states that he has not seen this in his own practice. By the criteria of Thorn and his associates[4-7,9,11] the subjective complaints, pigmentation, extreme hyponatremia and lack of eosinophil and 17-ketosteroid response to ACTH stimulation establish the diagnosis of adrenal insufficiency in this case. Highly purified ACTH gel was used intramuscularly as a test of adrenal response

because of its ease of administration. Thorn et al.[4-6] have found that changes in circulating eosinophils and in 17-ketosteroid and 17-hydroxycorticoid excretion after intramuscular administration of ACTH gel were comparable to those observed after the eight-hour intravenous infusion of ACTH in normal persons and in patients with Addison's disease. Thorn and his associates[5] state that the daily intramuscular injection of ACTH gel produces adrenocortical activation equal to or even greater than that resulting from the eight-hour intravenous infusion of an equivalent dose. They[4,5] found an average increase in 17-ketosteroid excretion of 8.7 mg. per twenty-four hours after two days of intravenous ACTH administration in 35 normal persons, with a range of increase of 4.7 to 16.0 mg. By this standard, the 3.3-mg. rise in urinary 17-ketosteroid excretion observed in the case reported above after seven days of ACTH administration indicates absent or greatly reduced adrenocortical function.

Whether adrenal insufficiency preceded or followed the cardiac infarct is uncertain. Substernal discomfort, nausea and drop in blood pressure, without eosinophilia, led to the dramatic episode of chest pain that was followed five days later by the "low-salt syndrome." This suggests that the myocardial infarction preceded the adrenal insufficiency. On the other hand, gastrointestinal distress, sleepiness and hypotension, together with an eosinophil count of 12 per cent just before the episode of severe chest pain, may mean that some adrenal insufficiency was present early in the course. It is of interest that pigment visible to the naked eye appeared in the scar about seventeen days after the infarction, since Huggins and Scott,[12] in their early case of adrenalectomy, observed pigmentation in the operative scars after the same interval. This suggests that the adrenal failure and infarction occurred at about the same time. Visible pigmentation usually does not occur in acute adrenal insufficiency when cortisone is given[13] although a spectrophotometrically detectable increase in pigment has been reported[14,15] after bilateral adrenalectomy in cortisone-treated cases.

The cause of the acute adrenal failure is also uncertain. The acute stress of myocardial infarction could conceivably precipitate an acute adrenal crisis in a patient with chronic insufficiency (Addison's disease), but in the case presented above, there were no symptoms nor signs of Addison's disease at the time of admission and the patient had tolerated two previous surgical procedures well. The normal electrocardiogram[16] on admission and the tolerance of relatively large doses of cortisone[17] are also evidence against pre-existing Addison's disease. It is conceivable that thrombosis, hemorrhage or even embolism of the adrenal glands occurred. Though hemorrhage from Dicumarol must be considered, it seems unlikely, since there were no signs of retroperitoneal hemorrhage or bleeding elsewhere, and the prothrombin level was never alarmingly low.

The prolongation of the PR interval that followed the myocardial infarction was marked and suggests the onset of adrenal insufficiency, since there is an increased occurrence of first-degree heart block in Addison's disease.[16-18] Lown et al.[19,20] also noted an increased prevalence of first-degree heart block in patients with Addison's disease and demonstrated that, on the whole, such patients have a prolonged PR whereas those with Cushing's disease have a shortened PR interval. The authors attribute this, in part, to the influence of C^{11}-oxysteroids. Lown, Ganong and Levine[20] also found that 25 per cent of 84 patients with acute myocardial infarction, during the first week of illness, have transient shortening of atrioventricular conduction time to levels of 0.12 to 0.13 second. These patients were presumably capable of a normal stress response.

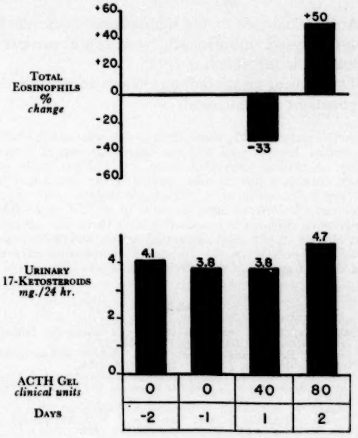

FIGURE 2. *ACTH Test, Showing Lack of Adrenocortical Response to Intramuscular Administration.*

The eosinophilia was striking in this case, particularly since no cause other than the myocardial infarct and adrenal insufficiency could be found. Recant et al.[21] report the range of eosinophil counts to be 94 to 1840 per cubic millimeter in 33 cases of Addison's disease. On one occasion the patient described above had an estimated total eosinophil count of 4000 per cubic millimeter (30 per cent of 100 cells counted in a total white-cell count of 16,150). Forssman, Hansson and Jensen,[22] in a series of cases of acute myocardial infarction, noted eosinopenia, with a gradual return to normal over a period of eight days. A majority of those patients studied showed an increase in twenty-four-hour 17-ketosteroid excretion.

It is possible that the eosinophilia in this case was part of the leukocyte response to myocardial infarction in the absence of adrenal-steroid production, suggesting that any eosinophilia in the presence of myocardial infarction warrants endocrine investigation.

Summary

An unusual case of the simultaneous occurrence of acute adrenal insufficiency and acute myocardial infarction is presented.

The clinical and laboratory observations and their implications are discussed.

In December, 1955, when the patient returned for follow-up studies, he was well and was taking 25 mg. of cortisone a day. A fasting eosinophil count was 712 per cubic millimeter, though a few months previously the count had been 219 per cubic millimeter. Serum electrolytes were normal. After the administration of 25 units of ACTH in an 8-hour intravenous drip for 5 consecutive days there was no significant change in the total eosinophil count, and there was no significant increase in the 24-hour 17-ketosteroid excretion. The thyroid uptake of radioactive iodine was 25 per cent.

References

1. Appelman, H. B. Addison's disease and myocardial infarction: case report. *Harper Hosp. Bull.* **11**:240-244, 1953.
2. Scribner, B. H., and Wiegert, H. T. Bedside determination of total base in serum. *J.A.M.A.* **155**:639-644, 1954.
3. Scribner, B. H., and Caillouttte, J. C. Improved method for bedside determination of bicarbonate in serum. *J.A.M.A.* **155**:644-648, 1954.
4. Thorn, G. W., et al. Pharmacologic aspects of adrenocortical steroids and ACTH in man. *New Eng. J. Med.* **248**:284-294, 323-337, 369-378, 414-423, 588-601 and 632-646, 1953.
5. Thorn, G. W., Goetz, F. C., Streeten, D. H. P., Dingman, J. F., and Arons, W. L. Teaching clinic: use of intravenous ACTH test in clinical practice. *J. Clin. Endocrinol.* **13**:604-613, 1953.
6. Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W. J., and Thorn, G. W. Use of ACTH in diagnosis of adrenal cortical insufficiency. *Am. J. Med.* **18**:3-14, 1955.
7. Thorn, G. W., Forsham, P. H., and Emerson, K., Jr. *The Diagnosis and Treatment of Adrenal Insufficiency.* 171 pp. Springfield, Illinois: Thomas, 1949.
8. Drekter, I. J., Pearson, S., Bartczak, E., and McGavack, T. H. Rapid method for determination of total urinary 17-ketosteroids. *J. Clin. Endocrinol.* **7**:795-800, 1947.
9. Renold, A. E., Jenkins, D., Forsham, P. H., and Thorn, G. W. Use of intravenous ACTH: study in quantitative adrenocortical stimulation. *J. Clin. Endocrinol.* **12**:763-797, 1952.
10. Thorn, G. W. Personal communication.
11. Thorn, G. W., et al. Advances in diagnosis and treatment of adrenal insufficiency. *Am. J. Med.* **10**:595-611, 1951.
12. Huggins, C., and Scott, W. W. Bilateral adrenalectomy in prostatic cancer: clinical features and urinary excretion of 17-ketosteroids and estrogen. *Ann. Surg.* **122**:1031-1041, 1945.
13. Huggins, C., and Bergenstol, D. M. Inhibition of human mammary and prostatic cancers by adrenalectomy. *Cancer Research* **12**: 134-141, 1952.
14. Thorn, G. W., et al. Clinical studies on bilateral complete adrenalectomy in patients with severe hypertensive vascular disease. *Ann. Int. Med.* **37**:972-1005, 1952.
15. Hall, T. C., McCracken, B. H., and Thorn, G. W. Skin pigmentation in relation to adrenal cortical function. *J. Clin. Endocrinol.* **13**:243-257, 1953.
16. Somerville, W., Levine, H. D., and Thorn, G. W. Electrocardiogram in Addison's disease. *Medicine* **30**:43-79, 1951.
17. Cleghorn, R. A., and Pattee, C. J. Teaching clinic: psychologic changes in three cases of Addison's disease during treatment with cortisone. *J. Clin. Endocrinol.* **14**:344-352, 1954.
18. Thorn, G. W., Dorrance, S. S., and Day, E. Addison's disease: evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. *Ann. Int. Med.* **16**:1053-1096, 1942.
19. Lown, B., Arons, W. L., Ganong, W. F., Vazifdar, J. P., and Levine, S. A. Adrenal steroids and auriculoventricular conduction. *Am. Heart J.* **50**:760-769, 1955.
20. Lown, B., Ganong, W. F., and Levine, S. A. Syndrome of short P-R interval, normal QRS complex and paroxysmal rapid heart action. *Circulation* **5**:693-706, 1952.
21. Recant, L., Hume, D. M., Forsham, P. H., and Thorn, G. W. Studies on effect of epinephrine on pituitary-adrenocortical system. *J. Clin. Endocrinol.* **10**:187-229, 1950.
22. Forssman, O., Hansson, C., and Jensen, C. C. Adrenal function in coronary thrombosis. *Acta med. Scandinav.* **142**:441-449, 1952.

SPECIAL ARTICLE

FLUORIDATION OF WATER SUPPLY

The Norway, Maine, Study

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AUGUSTA, MAINE

EXTENSIVE field and laboratory investigations have demonstrated that persons born and raised to about eight years of age on water supplies containing the optimum amount of fluorides experience significantly less dental decay throughout life than those born and raised to the same age on water supplies that are deficient in fluorides.[1-3] These studies have also demonstrated that the fluorides are as effective when they are added to the water supply by the water-works operator, at the water plant, as when they are added by nature, as the water flows over fluoride-bearing rock.[3]

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It has been properly pointed out[4] that the full benefits of the use of such a water supply during the period of tooth formation cannot be evaluated until the subject is ten to twelve years of age. The reason is that, although the crowns of all permanent teeth except the third molars have been formed by about the eighth year of life, eruption is not completed until the twelfth or thirteenth year.

Since the first permanent teeth do not erupt before the fifth year of life, an evaluation of the beneficial effects of such a water supply on permanent teeth cannot begin to be made until the subject is at least five years of age.

These facts have led to the popular assumption that it takes at least five years for the beneficial effects of the use of such a water supply to begin to become apparent. This is an unwarranted conclusion.

The exact mechanism by which fluorides result in resistance to dental decay is unknown. But the resistance appears to be partially, if not primarily, due to the incorporation of fluorides into the tooth structure while the enamel is being formed, producing an enamel that is less soluble by acids.[5,6]

In addition to this systemic effect, however, fluoridated water has a topical effect as it washes over the exposed crowns of erupted teeth.[7]

Although persons born and raised to about eight years of age on a fluoridated water supply receive the maximum dental benefits, because they are exposed to all the beneficial effects, it has been demonstrated that children beginning to use fluoridated water after some of the permanent teeth have erupted also receive some benefit.[3,7]

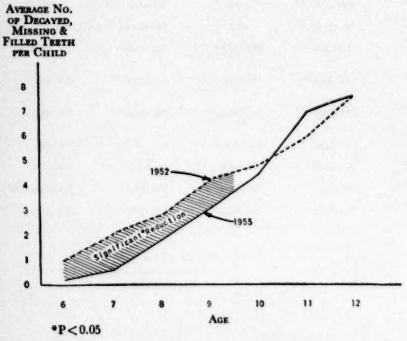

FIGURE 1. *Average Number of Decayed, Missing and Filled Permanent Teeth per Child Observed among Children Six to Twelve Years of Age (Norway, Maine, October, 1952, and April, 1955).*

PURPOSE

The purpose of this study was to determine whether or not the beneficial effects attributable to the use of fluoridated water begin to become apparent in less than five years.

MATERIAL

Norway is a town of about 3800 population, located in Oxford County, Maine. In 1945 its public water supply was found to contain a trace of fluorides.[8]

In October, 1952, the town began adding enough sodium silicofluoride to its water supply to maintain a total concentration of 1.0 parts of fluoride per 1,000,000 parts of water. In the same month, inspections were made of the teeth of all children enrolled in the elementary grades within the town schools, and in the two schools located on the outskirts.

TABLE 1. *Summary of Data on the Prevalence of Decayed, Missing and Filled Teeth among Children Six to Twelve Years of Age (Norway, Maine, October, 1952, and April, 1955).*

Age	No. of Children Inspected		No. of Decayed, Missing & Filled Permanent Teeth Found		Average No. of Decayed, Missing & Filled Permanent Teeth per Child		Percentage Change in Average No. of Decayed, Missing & Filled Permanent Teeth per Child
	1952	1955	1952	1955	1952	1955	
yr.							
6	37	17	36	3	1.0	0.2	−80
7	43	44	89	28	2.1	0.6	−71
8	50	54	141	102	2.8	1.9	−32
9	55	60	239	187	4.3	3.1	−28
10	52	45	248	202	4.8	4.5	Not statistically significant*
11	56	46	337	319	6.0	6.9	Not statistically significant*
12	52	47	398	358	7.6	7.6	Not statistically significant*

*P>0.05.

This outer area is not served by the Norway water supply. One of the outside schools, the Lake School, consists of a subprimary and first grade. After the

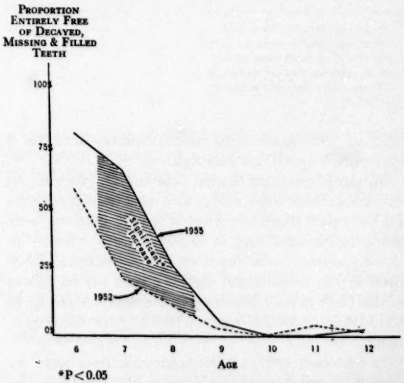

FIGURE 2. *Proportion of Children, Six to Twelve Years of Age, Entirely Free of Dental Decay in Permanent Teeth (Norway, Maine, October, 1952, and April, 1955).*

first grade, children from this school attend the town schools. Children from the other school in the outer

area, the Swift's Corner School, attend the town schools after the fifth grade.

In April, 1955, inspections were made of the teeth of all children enrolled in the elementary grades of the town schools, but not of the teeth of children attending the outlying schools.

Methods

All the inspections were made by a registered dental hygienist who has been with the official dental-health program for Maine since its inception in June, 1924, and all were made with mouth mirrors and No. 5 explorers, in good, natural light.

In the Elementary School Building, in Norway, all the inspections were made in a special office room. In the other three buildings where inspections were made in Norway, and in the outer-area schools, all the inspections were made in the classrooms. Children in the seventh and eighth grades attend school in the High School Building, in Norway. All of them were taken to the Elementary Building for the inspections.

In October, 1952, all the inspection data were recorded by members of the Norway Mothers Club. In April, 1955, all the inspection data were recorded by students in their junior year in high school, who were following the commercial curriculum. These data were processed by personnel of the Division of Dental Health and the Division of Research and Statistics of the State Department of Health and Welfare.

Age was recorded to the nearest birthday, as determined from school registration cards.

No water histories were taken.

Dental-Decay Rates

The prevalence of decayed, missing and filled permanent teeth observed in these inspections is summarized and compared in Table 1, and presented graphically in Figure 1.

Other studies have indicated that similar reductions in the average number of decayed, missing and filled permanent teeth per child have been experienced within similar periods after fluoridation was started in Rio Vista, California[9]; Coeur D'Alene[10] and Lewiston,[10,11] Idaho; Evanston, Illinois[12,13]; Marshall, Texas[14]; and Sheboygan, Wisconsin.[15,16] The data presented in the reports on these studies are summarized, and compared with the Norway data, in Table 2.

The Evanston, Illinois, data were stated to be statistically significant, but no information was given in the reports about the statistical significance of the other data. The Sheboygan, Wisconsin, data were averaged for all children in the seventh, eighth and ninth grades; no ages, or age distributions, were given, and the placement of these statistics in Table 2 is arbitrary.

Similar reductions have been reported after three years of fluoridation in Newburgh, New York.[17] The data were not included in Table 2 because they were reported on a "per 100 erupted-permanent-teeth"

Table 2. *Summary of Percentage Changes in Average Number of Decayed, Missing and Filled Permanent Teeth per Child Reported after Fluoridation in Other Communities,[9-18] Compared with Significant Data in Norway, Maine.*

Age	Rio Vista, Cal.		Coeur D'Alene, Idaho		Lewiston, Idaho		Evanston, Ill.	
	No. of children studied	Percentage change*	No. of children studied	Percentage change*	No. of children studied	Percentage change*	No. of children studied	Percentage change†
yr.								
6	52-68	−64	58-77	−55	No data	No data	461-765	−50
7	63-63	−37	58-130	−45	No data	−58	759-838	−32
8	54-62	−21	64-111	−41	No data	−35	771-440	−22
9	39-48	− 6	43-79	−29	No data	−25	No data	No data
10	41-58	− 3	42-62	−30	No data	No data	No data	No data
11	44-63	−27	35-60	−11	No data	No data	No data	No data
12	27-50	−35	22-14	−12	No data	No data	No data	No data
13	36-47	−14	No data	No data	No data	No data	No data	No data
14	No data	No data	No data	No data	No data	No data	No data	No data
15	No data	No data	No data	No data	No data	No data	No data	No data
16	No data	No data	No data	No data	No data	No data	No data	No data

*3 yr. after fluoridation started.
†12-22 mo. after fluoridation started.
‡30 mo. after fluoridation started.
§2 yr. after fluoridation started.
¶33 mo. after fluoridation started.
‖$P > 0.05$.

basis, rather than on a "per-child" basis. The average number of decayed, missing and filled permanent teeth per 100 erupted permanent teeth declined 62 per cent among children six to seven years old, 36 per cent among those eight to nine years old and 27 per cent among those ten to twelve years old. The reductions were stated to be statistically significant.

One at least partially comparable study in New Jersey[18] failed to disclose consistently similar reductions in the average number of decayed, missing and filled permanent teeth per child. In that study, examinations were made of the teeth of children in an area, in the southern portion of the State, where the drinking water naturally contained 1.1 to 2.4 parts of fluorides per 1,000,000 parts of water, and in 26 communities, in the northern part of the State, where there were no fluorides in the drinking water. The children in the area containing natural fluorides were divided into two groups: those who lived in the area both before and after their fourth birthday, and those who moved into the area after their fourth birthday. There is no way of telling precisely how long children in the latter group had been using the fluoride-bearing water at the time of the examinations. However, they presumably are somewhat comparable to the Norway children, at least at the ages of six and seven. The percentage differences in average numbers of decayed, missing and filled permanent teeth per child, between those who lived in the nonfluoride area and those who had moved into the fluoride area after their fourth birthday, are given in Table 3. The report is not clear on whether or not these differences are statistically significant.

Decay-Free Children

The proportions of Norway children entirely free of dental decay in permanent teeth are similarly summarized and compared in Table 4, and presented graphically in Figure 2.

Some of the studies previously referred to indicated that similar increases in the proportions of children entirely free of dental decay in permanent teeth have been experienced within similar periods after fluoridation was started in Rio Vista, California[9]; Coeur D'Alene, Idaho[10]; and Sheboygan, Wisconsin.[15,16] The data presented in the reports on these studies are summarized, and compared with the significant Norway data, in Table 5.

The earlier notations on the statistical significance of the data from the other communities, and on the placement of the Sheboygan, Wisconsin, data in the table, also apply to Table 5.

Table 2 *(Concluded).*

Age	Norway, Me.		Marshall, Tex.			Sheboygan, Wis.	
	No. of children studied	Percentage change‡	No. of children studied	Percentage change§	No. of children studied	Percentage change*	No. of children studied	Percentage change¶
yr.								
6	37-17	−80	61-54	−58	61-64	−48	No data	No data
7	43-44	−71	64-51	−40	64-53	−57	No data	No data
8	50-54	−32	44-58	−42	44-51	−36	No data	No data
9	55-60	−28	38-53	−33	38-54	−35	No data	No data
10	52-45	Not statistically significant‖	46-54	−20	46-50	−23	No data	No data
11	56-46	Not statistically significant‖	34-32	−11	34-52	− 4	No data	No data
12	52-47	Not statistically significant‖	41-34	−31	41-31	− 3	7th Grade	−19
13	No data	No data	40-45	−16	40-29	−18	8th Grade	
14	No data	No data	31-33	−14	31-43	−18	9th Grade	
15	No data	No data	19-35	−19	19-30	−12		
16	No data	No data	1-23	−38	1-31	−17		

*3 yr. after fluoridation started.
†12-22 mo. after fluoridation started.
‡30 mo. after fluoridation started.
§2 yr. after fluoridation started.
¶33 mo. after fluoridation started.
‖$P > 0.05$.

Discussion

Persons born and raised to eight or ten years of age on a water supply containing the optimum amount of fluorides receive the maximum protection against dental decay. The later in life one begins to use such drinking water, the smaller the amount of protection conferred.

In this study, age was recorded to the nearest birthday. This means that the average age of the children in each age group was six months younger than that of children in studies in which age was counted to the last birthday. Accordingly, this study tends to show greater reductions in the average number of decayed, missing and filled permanent teeth per child, and greater increases in the proportions of children entirely free of dental decay in permanent teeth, than studies in which age was counted to the last birthday. How great these differences may be, and even whether or not any such theoretical differences actually exist at particular ages, cannot be stated.

TABLE 3. *Percentage Differences in Average Numbers of Decayed, Missing and Filled Permanent Teeth per Child between Children in 26 Nonfluoride Communities in New Jersey and Children Who Moved into Fluoride Areas of New Jersey after Their Fourth Birthday.**

AGE	NO. OF CHILDREN EXAMINED		PERCENTAGE DIFFERENCE
	NONFLUORIDE COMMUNITIES	FLUORIDE COMMUNITIES	
yr.			
6	488	12	−88
7	599	28	+40
8	608	32	−25
9	566	43	− 3
10	561	35	−19
11	572	41	− 5
12	611	56	+ 6
13	566	47	+ 3
14	490	36	−28
15	376	33	−23
16	320	19	−43

*Based on data of Wisan.[13]

One should bear in mind, however, that the method of counting ages was not specified in the reports on any of the other communities except in New Jersey and in Newburgh, New York, where age was counted to the last birthday.

Because no water histories were taken in this study, it could be assumed that all the children inspected in April, 1955, had been using the fluoridated Norway water supply continuously since October, 1952. This is not true. The beneficial effects of fluoridation for children who used this water supply continuously during this period were undoubtedly reduced to the extent that children not served by the Norway water supply were included in the April, 1955, inspections. Since all children in the town schools were inspected at that time, it is quite obvious that some children coming from the Lake and Swift's Corner schools, and living in homes in the outer area of Norway, as well as some within the town of Norway served by private water supplies, were included in the April, 1955, inspections.

It cannot be said, however, that these children received absolutely no benefit from the fluoridated water. To the extent that most of their drinking was done during the waking hours of the day, when they were attending Norway schools served by the fluoridated water supply, they received some benefit — how much cannot be stated. The most that can be said is that the inclusion of these children minimized, rather than maximized, the beneficial results reported here.

Despite these general considerations, it is readily apparent that, in the short space of thirty months, fluoridation of the town water supply has produced statistically significant reductions in the average number of decayed, missing and filled permanent teeth among Norway children six to nine years of age, and statistically significant increases in the percentages of seven-year-old and eight-year-old Norway children entirely free of dental decay in permanent teeth.

At first, it may seem surprising to find such results among children who already had formed most of their erupted permanent teeth before fluoridation was started. It should be remembered, however, that part of the benefit of fluoridation has been demonstrated to be attributable to the topical effect of fluoridated water washing over the exposed crowns of erupted teeth.[7]

TABLE 4. *Summary of Data on the Proportions of Children Six to Twelve Years of Age Entirely Free of Dental Decay in Permanent Teeth (Norway, Maine, October, 1952, and April, 1955).*

AGE	NO. OF CHILDREN INSPECTED		NO. OF CHILDREN ENTIRELY FREE OF DECAY IN PERMANENT TEETH		PROPORTION OF CHILDREN ENTIRELY FREE OF DECAY IN PERMANENT TEETH		PERCENTAGE CHANGE IN PROPORTION OF CHILDREN ENTIRELY FREE OF DECAY IN PERMANENT TEETH
	1952	1955	1952	1955	1952	1955	
yr.					%	%	
6	37	17	22	14	59	82	Not statistically significant*
7	43	44	10	29	23	66	+187
8	50	54	6	15	12	28	+133
9	55	60	1	3	2	5	Not statistically significant*
10	52	45	0	0	0	0	—
11	56	46	2	0	4	0	Not statistically significant*
12	52	47	0	1	0	2	Not statistically significant*

*$P > 0.05$.

The amount of reduction in the average number of decayed, missing and filled permanent teeth per six-year-old and seven-year-old child appears to be considerably higher than that experienced in other communities except in New Jersey, where similar results were experienced among six-year-olds. This may not be as serious as it appears at first sight, however, since

the statistical significance of much of the other data is unknown. The most troublesome aspect is the failure of the Norway data to coincide more closely with the Evanston, Illinois, data, which are known to be statistically significant. On the other hand the Evanston data are consistently lower than those of all the other communities, not just the Norway data alone.

At eight and nine years of age, there is good agreement with the experience in other communities.

The increases in the proportions of children entirely free of dental decay in permanent teeth cannot be compared with the experience in other communities, because few data are available and their statistical significance is unknown.

TABLE 5. *Summary of Percentage Changes in Proportions of Children Entirely Free of Dental Decay in Permanent Teeth after Fluoridation in Other Communities, Compared with Significant Data in Norway, Maine.*[9,10,15,16]

AGE	RIO VISTA, CAL.		COEUR D'ALENE, IDAHO		NORWAY, MAINE		SHEBOYGAN, WIS.	
	NO. OF CHILDREN STUDIED	PERCENTAGE CHANGE*	NO. OF CHILDREN STUDIED	PERCENTAGE CHANGE*	NO. OF CHILDREN STUDIED	PERCENTAGE CHANGE†	NO. OF CHILDREN STUDIED	PERCENTAGE CHANGE‡
yr.								
6	52-68	+70	58-77	+29	37-17	Not statistically significant§	No data	No data
7	63-63	+63	58-130	+92	43-44	+187	No data	No data
8	54-62	+73	64-111	+484	50-54	+133	No data	No data
9	39-48	0	43-79	+600	55-60	Not statistically significant§	No data	No data
10	41-58	+40	No data	No data	52-45	Not statistically significant§	No data	No data
11	44-63	+ (infinite)	No data	No data	56-46	Not statistically significant§	No data	No data
12	27-50	+ (infinite)	No data	No data	52-47	Not statistically significant§	7th Grade	
13	36-47	+ (infinite)	No data	No data	No data	No data	8th Grade	+16
14	No data	No data	No data	No data	No data	No data	9th Grade	

*3 yr. after fluoridation started.
†30 mo. after fluoridation started.
‡33 mo. after fluoridation started.
§$P > 0.05$.

CONCLUSION

The beneficial effects attributable to the use of fluoridated water begin to become apparent thirty months, or less, after fluoridation is started in a community.

REFERENCES

1. American Association for the Advancement of Science. *Fluorine and Dental Health*. Edited by F. R. Moulton. 101 pp. Washington, D.C.: American Association for the Advancement of Science, 1942.
2. *Idem. Dental Caries and Fluorine*. Edited by F. R. Moulton. 111 pp. Washington, D.C.: American Association for the Advancement of Science, 1942.
3. *Idem. Fluoridation as a Public Health Measure*. Edited by J. H. Shaw. 232 pp. Washington, D.C.: American Association for the Advancement of Science, 1954.
4. Ast, D. B. Caries-fluorine hypothesis and suggested study to test its application. *Pub. Health Rep.* **58**:857-879, 1943.
5. American Dental Association. *Fluoridation in the Prevention of Dental Caries: A manual prepared by the Council on Dental Health*. 28 pp. Chicago: American Dental Association, 1951.
6. Maxcy, K. F., et al. *Report of the ad Hoc Committee on Fluoridation of Water Supplies. (National Academy of Sciences-National Research Council, Division of Medical Science*, Publication No. 214.) 8 pp. Washington, D.C.: National Academy of Sciences-National Research Council, 1952.
7. Bushel, A., and Smith, D. J. Newburgh-Kingston study, no. X: dental findings for 17-year-old group after nine years of fluoride experience. *New York J. Dent.* **25**:215-218, 1955.
8. Chemical characteristics of public water supplies. State Department of Health and Welfare, Augusta, Maine, June, 1945.
9. Reduction of tooth decay in Rio Vista results from fluoridation. *California's Health* **13**:4, 1955.
10. Walters, F. J. Preliminary report — Coeur D'Alene dental survey, 1955. *Idaho Dent. A. Newsletter* **4**:5, 1955.
11. Pelton, W. J. Unpublished data.
12. Stadt, Z. M. *Fluoridation: North America*. Mimeographed report, October 27, 1950.
13. Hill, I. N., Blayney, J. R., and Wolf, W. Evanston dental caries study. VI. Comparison of prefluoride with postfluoride caries experience of 6-, 7-, and 8-year-old children in study area (Evanston, Ill.). *J. Dent. Research* **29**:534-540, 1950.
14. Taylor, E. *Supplemental Report of Marshall Fluoridation Study*. Mimeographed report, Texas State Department of Health, Dental Division, February 15, 1954.
15. Mimeographed report, Sheboygan Health Department, 1950.
16. Bull, F. A. Control of dental caries by addition of fluorides to public water supplies. *J. Am. Dent. A.* **41**:146-151, 1950.
17. Ast, D. B., Finn, S. B., and McCaffrey, I. Newburgh-Kingston caries fluorine study. I. Dental findings after 3 years of water fluoridation. *Am. J. Pub. Health* **40**:716-724, 1950.
18. Wisan, J. M. Dental caries and fluorine-water. *Pub. Health News* **27**:642-649, 1946.

MEDICAL PROGRESS

ARTHRITIS RESEARCH*

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THE many reports on arthritis research that are reviewed here do not fall naturally into a pattern. For this reason the somewhat arbitrary subheadings of "pathology," "bacteriology" and "immunology" have been used to classify them for interpretation. Although this method of presentation tends to oversimplify a complex subject, this sequence, to a certain extent, recapitulates historical trends.

The first of these historical trends began with both descriptive and pathological investigations into the many types of joint changes broadly classified as "arthritis." It extended from the latter part of the nineteenth century into the third decade of this century, by which time progress in the semantics of arthritis had permitted the separation of many subtypes of joint disease. The separation of rheumatic fever from rheumatoid arthritis, septic arthritis and degenerative arthritis was a notable accomplishment. This period was dominated by taxonomic problems in medicine as well.

The second historical trend in arthritis research discussed here also had its origin in the latter part of the nineteenth century. It began with bacteriologic studies that reached their peak in the fourth decade of this century. This period was much concerned with both the direct and the more subtle relations between infections and arthritis. It subsided in 1940 coincident with World War II with the development of effective antibiotic therapy for infections and with the coming into the field of medical research of a new generation of workers.

The third historical trend in arthritis research is still in progress. This period, beginning before World War II, has been greatly stimulated by important findings in the study of rheumatic fever, as well as by new concepts in the field of immunology. Current studies on arthritis are further characterized by a particular interest in the nature of rheumatoid arthritis. Many efforts to simulate this important disorder in animals have been based on the thesis that finding a laboratory model of the disease will lead to an effective cure in man. Certain provocative likenesses created in the laboratory have kept a number of groups active in further exploration of this subject.

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DESCRIPTIVE PHASE OF ARTHRITIS RESEARCH

Arthritis in Man and Animals

Studies in paleopathology have shown that Eocene mammals, Miocene crocodiles and Pleistocene camels sometimes had a deforming arthritis.[1] The earliest evidence of arthritis in man has been found in bone remains of the Neanderthal race.[2] In more recent human material from Egypt, dating from 4000 B.C. down to the Christian era, the frequent presence of spondylitis has been noted.[3] The frequency and type of human arthritis, however, is as difficult to determine from modern surveys[4] as it is from these historical remains. Data available indicate that arthritis of one type or another occurs in approximately 9.3 per cent of the adults in the United States.[5] Osteoarthritis, which affects 80 per cent of people over fifty years of age, is the most common form of arthritis in man.[6] Rheumatoid arthritis, which occurs more often in the group eighteen to forty-five years of age[7] is much less frequent, but has received just emphasis because of its severity and tendency to occur during the prime of life. Its true incidence is probably much greater than is apparent, for it is known that many atypical cases are found for each classic example of the disease.[8]

Degenerative Arthritis

Pathological studies on animals in captivity have shown that, in the animal world as in man, osteoarthritis is also a dividend of the aging process. Extensive changes of osteoarthritis, quite like those seen in human beings, have been described by Fox[9] in elderly bears, hyenas and gorillas. It also has long been apparent that degenerative arthritis is in some way related to the trauma of use, either physiologic, as in the large joints of dinosaurs, or from excessive use, as in occupational phenomena. There are other factors as well, for age compounds this wear and tear in some persons more than in others. Axhausen[10] was one of the first experimenters to show that the production of local necrosis of cartilage in the knee joints of animals led to the changes seen in chronic hypertrophic arthritis. Necrosis of cartilage caused by ligation of the local blood supply will produce similar

changes.[11] Other studies in dogs[12] indicate that aseptic removal of a portion of knee cartilage will cause degenerative joint changes if the animal is allowed to use the joint promptly after the defect has been created. Surgical displacement of the patella in rabbits[13] and the spontaneous occurrence of this condition in man[13] also lead to osteoarthritis. Since recent writers have noted that cartilage regrowth is no more rapid when defects have been created in young subjects than when they have been created in old subjects,[13] these findings emphasize the need for adequate time to heal and for prompt corrective measures in many orthopedic conditions. It also points up the wisdom of using joints in work and in sports for the purposes to which they are best adapted.

An interesting approach to the question of other factors that precipitate degenerative joint changes has been supplied by the Silberbergs.[14] These workers find that a high-calorie, high-fat diet accelerates articular aging in certain strains of highly inbred mice.

Infectious Arthritis in Animals

The era of pathological studies on arthritis led to an early introduction to infectious arthritis as well. In domesticated animals, there are several examples of arthritis with clinical and pathological features simulating the pathological features of infectious arthritis in man. Goldberg[15] has described such a disease in cattle, and Collins and Goldie[16] have described a similar arthritis in swine. The latter authors were also able to produce the disease by experimental infection. Collins,[17] who has reviewed this subject in detail, points out the role of repeated small intravenous inoculations in bringing about a type of proliferative arthritis that mimics closely the local tissue changes seen in rheumatoid arthritis. Cultures of joint tissues and joint fluid in these chronic experimental lesions are usually sterile.

A similar type of spontaneous arthritis occurring in domesticated goats has been described by Pigoury.[18] This disease, which is called "agalactia" and is due to a pleuropneumonia coccobacillus, causes arthritis in 10 to 20 per cent of animals infected with this organism. It affects the radiocarpal, tibiofemoral and tibioastragaloid articulations a week after initial infection. Spontaneous remissions usually occur within two months. A somewhat similar spontaneous arthritis has been observed by Findlay et al.[19] in laboratory colonies of rats. This arthritis affects a small percentage of any given colony in which the pleuropneumonia organism is endemic. The disease can be reproduced by the injection of pleuropneumonia organisms into the joints or blood stream of this species. Pathological examination of these animals reveals a suppurative arthritis beginning in the synovial villi and soft tissues about the joints. Chronic lesions cause a destruction of cartilage and a connective-tissue proliferation. Unlike rheumatoid arthritis, this animal disease is usually self-limited and tends to heal. The importance of the L, or filterable phase, of the pleuropneumonia organism in promoting this infection has been stressed by various workers, who point out that the L form of these bacteria may survive in tissues even when cultures are sterile.

At least one form of arthritis in man is due to an L-forming bacteria. *Streptobacillus moniliformis* causes an acute arthritis in rat-bite fever due to this organism. This condition responds well to penicillin therapy.[20,21] It is also interesting that gold treatment alleviates the animal disease[22] as it does some examples of human rheumatoid arthritis.[23]

It has been believed that the clinical syndrome of Reiter's disease[24] with chronic arthritis, urethritis and uveitis could be due to an L-type of organism,[25] but this opinion has not been substantiated in more recent years. Attention has also been called to the fact that there are certain similarities between the clinical features of the chronic forms of Reiter's disease and rheumatoid arthritis.[26] Unfortunately, the difficulties in working with these organisms has greatly limited knowledge of their place in human medicine. At present there is no widely accepted evidence that these organisms are the cause of rheumatoid arthritis as it is known in man.

Bacteriologic Phase of Arthritis Research

Septic Arthritis

In 1884, Loeffler[27] gave intravenous injections of virulent living cultures of hemolytic streptococci to rabbits. Among other lesions produced was a septic arthritis. In 1913, Jackson[28] studied the pathology of joint lesions caused by the intravenous injection of virulent cultures of beta-hemolytic streptococci. She found that the first evidence of arthritis was an independent trapping of organisms in the synovial villus of the soft tissues about the joint, as well as in the joint cavity. In the course of a day or two, depending on the virulence, these loci spread to the surrounding tissues. She found that septic arthritis followed large infecting doses of streptococci, whereas a small dose of virulent organisms tended to form lesions restricted to the synovial villus and periarticular tissues, resulting in a more chronic type of arthritis. Intravenous injection of larger numbers of less virulent streptococci caused a similar, but a more persistent, arthritis. Two years later, Faber[29] repeated and extended these studies, and, in 1923, Swift and Boots[30] carried out similar experiments. In 1940, Cecil,[31] reporting for his group, described experiments in which the knee joints of rabbits were "sensitized" by intra-articular injections of killed "green" streptococci (alpha-hemolytic streptococci). Thereafter, when living cultures of the same organism were given intravenously, bacteria lodged more readily in the prepared than in the control joints. This joint sensitization was not bacterial strain specific, since it could be produced by other species of streptococci. These observations were repeated with both dead streptococci and strepto-

coccus nucleoprotein to sensitize the knee joints.[32] It was found that sensitized joints were more susceptible to arthritis after intravenous injections of living streptococci than after intravenous injections of living staphylococci. Control studies with joints pretreated with horse serum were also more susceptible to arthritis after living streptococci had been injected intravenously.[31] In still other studies, lesions similar to those seen in rheumatoid arthritis were produced in rabbits by Jordan[33] by intra-articular injections of either pneumococci or even with small amounts of turpentine. The nonspecificity of these inflammatory changes caused by several agents has been emphasized by Keefer and his group[34] as well.

During this period of interest in the streptococcal etiology of rheumatoid arthritis, Rothbard[35] used streptococci to produce arthritis in a somewhat different manner. He found that a more prolonged form of migratory polyarthritis followed intravenous injections of cultures of Group A, beta-hemolytic streptococci in the rat, a species normally resistant to this organism. Intermittent sepsis accounted for new joint lesions, which continued to appear for eight days. Similar experiments by Angevine and Rothbard[36] with the rabbit have added a different facet to these studies with streptococci. A tendency for the structures of the synovial villi and the ciliary process of the eye to trap infecting organisms was noted. In pathological studies on the rabbit type of streptococcal arthritis, Cecil et al.[32] found that the more chronic lesions were characterized by small round-cell infiltration. This type of lesion was produced by cultures of streptococci, pneumococci, staphylococci and paratyphoid A.

In all the experiments described above, arthritis resulted from direct invasion of the joint tissues by an irritating agent. Sensitization of the joint appeared to be a contributing, but not the critical, factor in inducing arthritis.

Taken together, these studies extending over half a century indicate that once bacterial bodies, or other irritating substances, reach the joint synovia, arthritis will follow. When the arthritis is chronic, it is difficult to distinguish the microscopical and pathological picture of one etiologic type from another. In some cases, bacteria reach the joint via the blood stream by virtue of their viability and their virulence. In other cases, less virulent bacteria given in greater numbers also cause arthritis. In all three types of study the degree of pathological change is related to the number of bacteria that reach, or grow in, the joint tissues.

Streptococci and Rheumatic Fever

Before the immunologic aspects of experimental arthritis are discussed, it is appropriate to review briefly one form of human arthritis in which there can be little doubt that the streptococcus plays a critical role. This is done to add perspective to the foregoing studies on experimental infectious arthritis.

A major dividend from past efforts to relate streptococcus infections to one or another form of arthritis has been the separation of such conditions as rheumatic fever and erythema nodosum from septic arthritis and from rheumatoid arthritis, with which they were once confused. The provocative role of streptococcal pharyngitis in acute rheumatic fever was emphasized by Griffith[37] in 1926 and by a number of workers in the decade that followed.[38-43] Gibson and Thomson[44] and Goldie,[45] among others, have demonstrated a rise in streptococcal antistreptolysin and streptococcal precipitin titers during rheumatic attacks. Collis, Sheldon and Hill,[46] as well as Gibson and McGibbon,[47] have indicated that delayed-type skin reactions to streptococcus proteins occur regularly in rheumatic fever. More recently, Wilson et al.[48] have carefully described the hereditary features of the rheumatic state. In the laboratory, Klinge[49] has produced lesions simulating rheumatic endocarditis and Aschoff nodules in rabbits by intravenous injections of foreign protein. In this decade, Murphy and Swift[50] have made a more exact model of rheumatic fever in animals with multiple skin infections with serologically different strains of virulent streptococci, and finally, the importance of a sequence of streptococcal infections in the induction of rheumatic attacks in man has been pointed out by Rantz, Boisvert and Spink.[51]

It is now known that although in the susceptibie rheumatic subject rheumatic fever may follow this type of exposure, his immune and allergic responses to streptococcal infections and to other antigenic stimuli are normal.[46,52,53] On the other hand, if streptococcal infections are blocked with prophylactic antibacterial therapy, rheumatic fever can be prevented.[54,55] All this evidence indicates that there is some common factor in many strains of Group A, beta-hemolytic streptococci that is the "external antigen" of rheumatic fever for certain hereditarily predisposed persons.

Streptococci in Rheumatoid Arthritis

It is only natural that epidemiologic and bacteriologic evidence that related streptococcal infections to rheumatic fever should have led to a parallel search for a similar association between streptococcal infections and rheumatoid arthritis. These efforts can be grouped most conveniently into three general types of study.

The first of these was an effort to demonstrate, in patients with rheumatoid arthritis, a direct invasion of the joint by micro-organisms. As early as 1913, Billings[56] had popularized the role of chronic septic foci, usually due to infection with the gamma or alpha streptococcus about the teeth and in the respiratory tract, as the cause of disease in remote parts of the body. This concept appealed to students of arthritis, who knew that erysipelothrix infections of swine,[16] for example, localize in the joints after transient

sepsis. It was reasoned that the same situation obtains in human rheumatoid arthritis. It was reasoned further that since the few organisms that can be harbored in the joint tissues in the animal disease, without detection by ordinary laboratory means, will keep the disease active, this was true in rheumatoid arthritis. In pursuit of this hypothesis, workers in Cecil's laboratory looked for transient bacteremias. This they did by culturing 20-ml. to 30-ml. samples of blood from which the serum was removed to prevent antibodies from inhibiting growth. They found attenuated organisms (alpha and gamma streptococci) in 61 per cent of 78 patients with rheumatoid arthritis.[57] Gray and Gowen[58] likewise found streptococci in the blood of 62 per cent of 71 patients with rheumatoid arthritis. This extraordinary frequency of positive findings was not confirmed by many other workers. Margolis and Dorsey, culturing the blood,[59] the joint fluid and biopsy specimens[60] from patients with rheumatoid arthritis, found streptococci that they thought were significant in some of these cultures. Still others were even less successful with cultures of synovial fluid[61] and tissues.[62] Modern bacteriologists will be quick to point out that during this period, in which streptococci were being cultured so freely, methods of medical bacteriology left much to be desired.

In the late 1930's and early 1940's, this whole subject of the direct culturing of patients with rheumatoid arthritis was re-explored with improved methods. Aerobic, anaerobic and high-protein-medium cultures, embryo-egg inoculations and animal inoculations were done with blood, rheumatic nodules, synovial fluid and joint biopsy material. The earlier findings of streptococci in body fluids and tissues could not be confirmed.[63] Among these negative studies were those of Sabin[64] and Preston,[65] who searched for the pleuropneumonia and L-forming organisms as well. Eventually, these authors came to the conclusion that occasionally, alpha-hemolytic streptococci appear in the blood stream and tissues of patients with rheumatoid arthritis and in other diseases as well. Their special methods did not indicate that human rheumatoid arthritis was due to any of the esoteric organisms that cause arthritis in animals.

It is interesting that chemotherapeutic agents were coming into wide use at this juncture in the change of results. It is also interesting that, at about this time, Okell and Elliott[66] were reporting alpha-hemolytic streptococci in as many as 10 per cent of blood cultures from patients studied before tooth extraction, a frequency that is not now observed in the antibiotic era.[67] The usual explanation given for the difference between past and present cultural results is that the former procedures were multiple-transfer technics open to many chances for contamination. People who have handled human cultural material in the laboratory for years will wonder at this explanation, since alpha and gamma streptococci are unusual contaminants when there is a break in technic. We do know that the septic types of arthritis due to transient bacteremia (*Escherichia coli*, pneumococci and streptococci) have almost disappeared from the wards of teaching hospitals.

The second type of study has been a search for an indirect relation between streptococcal infections of the teeth and respiratory tract and attacks of rheumatoid arthritis. To date, the cultural results from this approach have been no more impressive than those from the direct method. Although infections with beta-hemolytic streptococci may precede rheumatoid arthritis, they are an unusual precursor to acute attacks. A negative history, without laboratory work, of respiratory infection preceding rheumatoid arthritis, however, is of little significance. Equally unreliable is a negative history of pharyngitis in establishing the relation between hemolytic streptococci and rheumatic fever or nephritis.

The third type of evidence that has been cited to implicate streptococcal infections in rheumatoid arthritis has been that of serologic and hypersensitivity data. In syphilis and brucellosis, in which it is most difficult to recover organisms from the patient, serology is of importance in diagnosis and treatment. In tuberculosis, in which both cultures and antibody technics may be of little value, responses to tuberculin are useful in diagnosis.

Both serologic and skin-test data indicate that patients with rheumatoid arthritis harbor one or another streptococccal infection. The appearance of streptococcal agglutinins in the patient's blood,[68] usually late in the course of active rheumatoid arthritis,[69] has been noted in 60 to 80 per cent of patients with the disease. No similar occurrence has been reported in other protracted illnesses. Heterophil antibodies to sheep cells also may appear in the course of rheumatoid arthritis.[70] The significance of each of these phenomena is not known.

Delayed-type skin reactivity to streptococcus proteins is even more frequent than serologic evidence of a streptococcal infection in patients with rheumatoid arthritis. Normal subjects show less frequent sensitivity reactions.[45] Sensitivity to other bacterial proteins (pneumococci, staphylococci and enterococci) does not occur regularly in patients with rheumatoid arthritis. This subject is made even more puzzling by the observation that in the more acute phases of rheumatoid arthritis, there may be a period of specific anergy to streptococcus proteins.[45] The same type of temporary anergy to delayed-type bacterial allergy has been reported in acute rheumatic fever,[46] in subacute bacterial endocarditis during sepsis,[71] in acute brucellosis in the period of intermittent sepsis[72a,72b,72c] and in overwhelming tuberculosis.[73] In these examples of skin-test anergy, it is assumed that specific desensitizations by homologous organisms or their protein products account for loss of sensitization. So-called "anticutin," which occurs in sarcoid and lymphomas,[74] may be another explana-

tion for this curious phenomenon, and there may be other mechanisms as well. Since patients with rheumatoid arthritis are not anergic to nonstreptococcal sensitivity systems such as tuberculin sensitization, unless treated with cortisone,[75] these data support the concept that biologically significant streptococcal infections are common in the course of rheumatoid arthritis. Whether they are causally related is another question.

This story would not be complete without some mention of the role of alpha-hemolytic streptococci in serologic and skin-test responses. Agglutinins and positive skin tests can be induced by alpha-hemolytic, as well as beta-hemolytic, streptococci,[76] by virtue of some degree of crossantigenicity[76,77] existing among the streptococcal families. A great many people both with and without rheumatoid arthritis harbor chronic infections due to these organisms. This is particularly true in the age groups in which rheumatoid arthritis is common. That they are not entirely benign infections is attested to by their occasional capacity to cause erythema nodosum,[78] iritis[79] and subacute bacterial endocarditis. In fact, stirring up infected areas about the teeth, in the pharynx or in the bronchi is rarely associated with a flare-up in rheumatoid arthritis.[80]

These many observations on the presence of one or another streptococcal infection coincident with rheumatoid arthritis do not mean that they are related etiologically. Nor does the fact that many teeth and tonsils have been removed without benefit to patients with rheumatoid arthritis[80] mean that they are not related phenomena. It will be remembered that before accurate knowledge about the role of hemolytic-streptococcus infections, tonsillectomy was once in vogue for the cure of rheumatic fever. The subtleties of host-parasite relations, if indeed rheumatoid arthritis is such a condition, are not to be solved by a primitive casting out of these grossly visible symbols of deep-seated infectious processes.

Gold Therapy and Experimental Arthritis

The use of gold compounds in medicine has had its champions in times past as well as its recent advocates in the therapy of rheumatoid arthritis. Gold therapy was used as early as 1924 for the treatment of tuberculosis,[81] in which it was regarded as an antimicrobial agent. During the next twenty-five years a series of studies on the effect of gold salts on experimental streptococcal infections in animals was reported. It was found that these compounds had antibacterial properties both in vitro and in vivo. Pneumococcal,[82] streptococcal,[82-85] syphilitic[85] and pleuropneumonialike[86,87] infections were successfully treated. Of the many compounds used, sodium autothiomalate was most favored.[85,88] Pharmacologic studies indicated that, in experimental streptococcal arthritis[85] and "L" arthritis,[86] therapeutic responses followed pharmacologic dynamics similar to those of chemotherapeutic agents like the sulfonamides, which were used for control studies. When gold salts could be kept in solution for in vitro tests,[85] direct bactericidal properties were demonstrated that corresponded to blood levels obtained in successfully treated animals.[88] Streptococcal arthritis due to more virulent organisms[88] was affected less by gold therapy than by the more potent sulfonamides of the time.

Apparently, these favorable effects of gold treatment on experimental arthritis depended not only on adequate blood and tissue levels of the compound at the critical times of joint invasion but also on the duration of therapy. At these junctures, they were active even when the reticuloendothelial system was blocked with India ink or methylene blue.[88] However, like the less potent antibiotics, gold compounds were relatively ineffective in the therapy of long-entrenched experimental joint infections.[86,88]

Interest in gold treatment for human rheumatoid arthritis stems directly from these extensive animal investigations and the popular belief, at that time, that rheumatoid arthritis was due to some type of infectious process. Its use now in arthritis has lingered on long after the introduction of more effective antibiotics and chemotherapeutic agents have displaced it in the field of infectious diseases.[89]

Perhaps a proper opinion to hold concerning the role of infection in rheumatoid arthritis, in the absence of more sound knowledge on the subject, should be to maintain an open mind and make an effort to separate fact and fancy. The many immunologic features that characterize rheumatoid arthritis should arouse continued curiosity.

Immunology of Experimental Arthritis

Autotissue Antibodies and Arthritis

The concept that arthritis may not be due to some obscure infection, but rather may be a manifestation of allergy to joint tissue, has recently become popular. This attractive hypothesis suggests that, for some unknown reason, the host becomes allergic to antigens present in joint tissues. In turn, the reaction that follows in the joint causes arthritis and the release of more joint antigen, thus setting up a self-perpetuating pathologic process. Pursuit of this hypothesis has taken two forms. The first presupposes an external factor that alters joint tissue in such a way that it becomes antigenic. The second presupposes that the host in some way becomes allergic to his own normal joint tissues without the intervention of an external "adjuvant" antigen. There is some precedent in experiments on other "organ lesions" for the first of these thoughts, but none for the latter.

Immunologists have long wondered over the multiplicity of organ antigens that occur in the animal body without inducing autoimmune responses. Any of these is an excellent antigen for a heterologous species, and even for a homologous host of the same

species, as witnessed by the problems faced by the surgeon attempting homotransplantation.* So far, there is no clear evidence that a given type of organ pathology in man is caused by immunity to his own tissues independent of an external antigenic stimulus.

There are several examples of experimental organopathies that can be produced in the manner suggested by the first hypothesis. The most widely known of these is nephrotoxic nephritis.[97,98] When the renal tissue of one species is used to immunize a different species, it is found that no nephritis occurs in the animal immunized, but nephritis is produced when immune serum from the heterologous animal is given to the species from which the original kidney antigen was obtained. This "nephrotoxic nephritis" has been studied in a number of different interspecies systems, the most popular being with antirat-kidney rabbit serum. When potent nephrotoxic serum is tagged with I^{131}, is is found to localize in many organs in the host as well as in the glomerular basement membrane.[99] If an antibody response to this foreign protein is blocked by x-rays,[100] no subsequent nephritis develops. Control antiserums prepared to other organs are not nephrotoxic. Furthermore, when the renal circulation is blocked for a short time coincident with the injection of antikidney serum, no nephritis or I^{131}-tagged localization takes place in the kidney that was temporarily excluded from the circulation.[99] Although these findings are clear evidence that nephrotoxic nephritis is an immunologic phenomenon, they do not indicate that nephritis as it is known in man is an endogenous autodestruction of kidney tissue independent of an external toxic and antigenic cause. On the contrary, current opinion of the pathogenesis of nephritis emphasizes the direct toxic nature of specific strains of beta-hemolytic streptococci for certain kindred as the cause of human glomerulonephritis.[101]

In spite of discrepancies between experimental and natural nephritis, the nephrotoxic model has had a considerable influence on laboratory methodology in many fields of medicine. In 1930, Burky[102] reproduced, in rabbits sensitized with homologous lens tissue and staphylococcal filtrates, the condition known as "phaco-anaphylactica" in human beings. Autoantibodies in other eye diseases have also been postulated. The role of autosensitization to choroid pigment in sympathetic ophthalmia was first studied by Elschnig.[103] A delayed-type skin test to choroid pigment derived from many species appears in persons with eye injuries, in some of whom sympathetic ophthalmia developed.[104] Various workers have pointed out that damage to the choroid from within the host, such as by tumors, does not cause sympathetic ophthalmia. Sympathetic ophthalmia seems to require a puncture wound of the eye, which, it can be said, permits an external antigen to set the pathologic process in motion. This need for an external source of an antigen in these specific organopathies runs as a recurring theme through these studies.

Other tissue disorders that have been studied with antiorgan serum have been an experimental encephalomyelitis[105] somewhat like multiple sclerosis and an experimental orchitis, resulting in interference with spermatogenesis but not with the endocrine functions of the gonads.[106]

The accessibility of the formed elements of the blood to experimental manipulation has yielded a whole series of interesting anticell antibody phenomena.[107] It is now known that purpura can be produced by antiplatelet antibodies made in a different host[108] and that sedormid purpura is the result of an antibody to the drug capable of destroying platelets that have adsorbed the drug.[109] In this system, normal platelets, as well as those of the affected person, are specifically lysed when exposed to sedormid and specific antiserum.[110,111] Here, the drug has acted as the external adjuvant. When it is withdrawn, purpura ceases. Antibodies can be developed not only to platelets[112] but also to lymphocytes[113] and to neutrophils.[107] Furthermore, a similar system is responsible for the destruction[114] or the agglutination[115] of leukocytes in tuberculin hypersensitivity. Each of these phenomena is likewise dependent on an "adjuvant" antigen or hapten. The leukophagocytosis of the L. E. test, which can be passively transferred in vitro to normal cells, might seem to be an example of an autoantibody not dependent on an external antigenic stimulus. It is likely that it is not the result of an anticell antibody of the type under discussion, where a healthy cell is the target for injury, but rather an opsonin for leukocyte débris resulting from some other mechanism of injury. The nonspecificity of the L. E. test found in a number of unrelated pathologic conditions is consistent with this interpretation.[116]

Antijoint Antibodies

Efforts to produce experimental arthritis by immunization of animals with joint tissues have been made in several laboratories. McKee and Swineford[117] immunized guinea pigs and rats with homologous joint and kidney tissue combined with heat-killed beta-hemolytic streptococci. No precipitating antibodies or pathologic abnormalities in joint or other organs resulted. Glynn and Holborow[118] were able to cause a synovitis in rabbits by immunizing them with chondroitin sulfate from human costal cartilage

*In the "lower" forms of animal life, such as insects, which depend for survival on their own fecundity as their chief means of dealing with parenteral parasites, immune responses to foreign antigens are much less complex than in warm-blooded species. In contrast to mammals, insect homotransplantation can be accomplished with regularity, and is the basis for modern knowledge of insect endocrinology.[92] It is somewhere at the level of the salamander that a proportion of homografts are rejected. In mammals, tissue homotransplantation is possible only very early, in postnatal or in embryonic life, before the immunologic system is developed. Except in genetically similar twins,[93] in certain twins among animals[92] and in rare spontaneous examples of human beings with two blood types,[93] the cells of one host will not long prosper in a foster host. Much evidence has been amassed to indicate that this rejection of tissues is an immunologic phenomenon.[94,95] It is known, for example, that a human being who has a virtual absence of gamma globulins will accept a skin homograft,[96] whereas homografts are regularly rejected by the normal person.

combined with live beta-hemolytic streptococci. In view of the ability of beta-hemolytic streptococci alone to cause joint lesions in rabbits, this finding bears little significance. Favour and his co-workers[119] recently followed the experimental nephrotoxic nephritis model somewhat more closely than has been done heretofore, in efforts to produce experimental arthritis. They immunized rabbits with guinea-pig synovia. They also immunized guinea pigs with guinea-pig synovia. Each type of experiment was done with and without adjuvants added to the synovial antigen. Antijoint serum fractionated to yield high-potency material for intra-articular injection in a concentrated form was prepared. Both antijoint serum and the fractions of antijoint serum were tagged with I^{131} and given either intravenously or intra-articularly to guinea pigs. No evidences of specific localization of the tagged materials on joint tissue and no synovial lesions were found in recipient animals.

In the foregoing series of observations on the immunology of arthritis, experimental arthrotoxic arthritis has been found to be an even more nebulous entity than is experimental nephrotoxic nephritis. At least, nephrotoxic nephritis can be produced regularly in the laboratory, even though it is not a model of spontaneous glomerulonephritis in man. It is perhaps significant that both experimental organopathies of the laboratory and the clinical syndromes of man that appear to be examples of immunity to the host's own tissues are dependent on the intervention of an external foreign substance. Like examples of arthritis caused by bacteria, tissue damage seems to depend first on the presence of the inciting agent at the site of tissue injury.

* * *

This story — like a Japanese print without borders — has no conclusion.

If there is to be any conclusion from the experimental data reviewed, it is that much more research in arthritis is needed. The pattern of past findings indicates that one profitable future approach may be a further study of factors that condition localization of irritating or antigenic substances in structures like the synovial villi or uveal tract of the arthritic patient. This is not the direction in which much arthritis research is now going. Current attention is being paid largely to various toxic methods of suppressing the normal immune response of the host. Although anti-inflammatory agents have been improved so that symptomatic treatment of active arthritis is less hazardous than in the past, present treatment leaves much to be desired. It is not surprising that the continued quest for methods of treating arthritis, based on blocking normal inflammatory and immune responses, has created more problems than it has solved.

References

1. Moodie, R. L. *The Antiquity of Disease*. 148 pp. Chicago: University of Chicago Press, 1923. Pp. 161-221.
2. Boule, M. L'homme fossile de la Chapelle-aux-Saints (Corrèze). *Ann. de paleontol.* **6**:109, 1911.
3. Sigerist, H. E. *A History of Medicine*. Vol. 1. *Primitive and Archaic Medicine*. 564 pp. New York: Oxford University Press, 1951.
4. *Health Inquiry on Arthritis, Rheumatism, Diabetes and Tuberculosis: Hearing before the Committee on Interstate and Foreign Commerce, House of Representatives, Eighty-third Congress, October 5, 7, and 8, 1953*. 605 pp. Washington, D.C.: Government Printing Office, 1953.
5. Woolsey, T. D. Prevalence of arthritis and rheumatism in United States. *Pub. Health Rep.* **67**:507, 1952.
6. *Health Inquiry on Arthritis, Rheumatism, Diabetes and Tuberculosis*.[4] P. 461.
7. *Health Inquiry on Arthritis, Rheumatism, Diabetes and Tuberculosis*.[4] P. 467.
8. Cobb, S., Merchant, W., and Warren, J. Epidemiologic look at problem of classification in field of arthritis. *Ann. Rheumatic Dis.* **13**:361, 1954.
9. Fox, H. Chronic arthritis in wild mammals. *Tr. Am. Phil. Soc.* **31** (Part 2):73-148, 1939.
10. Axhausen, G. Kritisches und Experimentelles zur Genese der Arthritis deformans, insbesondere über die Bedeutung der aseptischen Knochen- und Knorpelnekrose. *Arch. f. klin. Chir.* **94**:331-351, 1911.
11. Wollenberg, G. A. Die Aetiologie der Arthritis deformans im Lichte des Experimentes. *Arch. f. orthop. u. Unfall-Chir.* **7**:226-234, 1909.
12. Fisher, A. G. T. Contribution to pathology and aetiology of osteo-arthritis: with observations upon principles underlying its surgical treatment. *Brit. J. Surg.* **10**:52-80, 1922-1923.
13. Bennett, G. A., and Bauer, W. Joint changes resulting from patellar displacement and their relation to degenerative joint disease. *J. Bone & Joint Surg.* **19**:667-682, 1937.
14. Silberberg, M., and Silberberg, R. Degenerative joint disease in obese and non-obese mice in strain Y'. Presented at the Second Interim Scientific Session of the American Rheumatism Association, Bethesda, Maryland, December 9, 1955.
15. Goldberg, S. A. Pathology of arthritis. *Am. J. Clin. Path.* **14**:1-23, 1944.
16. Collins, D. H., and Goldie, W. Observations on polyarthritis and on experimental erysipelothrix infection of swine. *J. Path. & Bact.* **50**:323-353, 1940.
17. Collins, D. H. *Pathology of Articular and Spinal Disease*. 331 pp. Baltimore: Williams & Wilkins, 1950.
18. Pigoury, L. L'agalaxie contagieuse de la chèvre au liban. *Bull. Soc. path. exot.* **31**:194-199, 1938.
19. Findlay, G. M., Mackenzie, R. D., MacCallum, F. O., and Klieneberger, E. Aetiology of polyarthritis in rat. *Lancet* **2**:7-10, 1939.
20. Altemeier, W. A., Snyder, H., and Howe, G. Penicillin therapy in rat bite fever. *J.A.M.A.* **127**:270-273, 1945.
21. Weber, R. A., and Favour, C. B. Rat-bite fever due to Streptobacillus moniliformis treated with penicillin: case report. *Bull. Johns Hopkins Hosp.* **77**:132-139, 1945.
22. Findlay, G. M., MacKenzie, R. D., and MacCallum, F. O. Chemotherapeutic experiments on pleuropneumonia-like organisms in rodents. *Brit. J. Exper. Path.* **21**:13-22, 1940.
23. Thompson, H. E., and Rowe, H. J. Cortisone and gold therapy in chronic rheumatoid arthritis. *Ann. Int. Med.* **36**:992-1000, 1952.
24. Reiter, H. Ueber eine bisher unerkannte Spirochäten-infektion (Spirochaetosis arthritica). *Deutsche med. Wchnschr.* **42**:1535, 1916.
25. Vallee, B. L. Reiter's disease: review of literature with presentation of case. *Arch. Int. Med.* **77**:295-306, 1946.
26. Wallerstein, R., Vallee, B. L., and Turner, L. Possible relationship of pleuropneumonia-like organisms to Reiter's disease, rheumatoid arthritis and ulcerative colitis. *J. Infect. Dis.* **79**:134-140, 1946.
27. Loeffler, A. F. Untersuchungen über die Bedeutung der Mikroorganismen für die Enstehung der Diphtherie beim Menschen, bei der Taube und beim Kalbe. *Mitt. a. d. k. Gesundheit.* **2**:451-499, 1884.
28. Jackson, L. Experimental streptococcal arthritis in rabbits: second study dealing with streptococci from milk epidemic of sore throat in Chicago, 1911-12. *J. Infect. Dis.* **12**:364-385, 1913.
29. Faber, H. K. Experimental arthritis in rabbit: contribution to pathology of arthritis in rheumatic fever. *J. Exper. Med.* **22**:615-628, 1915.
30. Swift, H. F., and Boots, P. H. Question of sensitization of joints with non-hemolytic streptococci. *J. Exper. Med.* **38**:573-598, 1923.
31. Cecil, R. L. Present trends in study of arthritis and rheumatism (Mayo Foundation Lecture). *Minnesota Med.* **23**:533-542, 1940.
32. Cecil, R. L., Angevine, D. M., and Rothbard, S. Experimental arthritis in rabbits produced with Streptococci and other organisms. *Am. J. M. Sc.* **198**:463-475, 1939.
33. Jordan, E. P. Synovial membrane and fluid in rheumatoid arthritis. *Arch. Path.* **26**:274-288, 1938.
34. Keefer, C. S., Parker, F., Jr., and Myers, W. K. Histologic changes in knee joint in various infections. *Arch. Path.* **18**:199-215, 1934.
35. Rothbard, S. Experimental arthritis in albino rat produced by group A hemolytic streptococcus. *Proc. Soc. Exper. Biol. & Med.* **44**:379-381, 1940.
36. Angevine, D. M., and Rothbard, S. Significance of synovial villus and ciliary process as factors in localization of bacteria in joints and eyes of rabbits. *J. Exper. Med.* **71**:129-136, 1940.
37. Griffith, F. Types of hemolytic streptococci in relation to scarlet fever. *J. Hyg.* **25**:385-397, 1926.

38. Schlesinger, B. Relationship of throat infection to acute rheumatism in childhood. *Arch. Dis. Child.* **5**:411-430, 1930.
39. Glover, J. A., and Griffith, F. Acute tonsillitis and some of its sequels: epidemiological and bacteriological observations. *Brit. M. J.* **2**:521-527, 1931.
40. Sheldon, W. On acute rheumatism following tonsillitis. *Lancet* **1**: 1337-1341, 1931.
41. Kuttner, A. G., and Krumwiede, E. Observations on effect of streptococci upper respiratory infections on rheumatic children: 3 year study. *J. Clin. Investigation* **20**:273-287, 1941.
42. Coburn, A. F. *The Factor of Infection in the Rheumatic State.* 228 pp. Baltimore: Williams & Wilkins, 1931.
43. Collis, W. R. F. Bacteriology of rheumatic fever. *Lancet* **2**:817-820, 1939.
44. Gibson, H. J., and Thomson, W. A. R. Study of aetiology of acute rheumatism, with special reference to relationship of haemolytic streptococcus to disease. *Tr. Med.-Chir. Soc., Edinburgh* **112**:93-116, 1933.
45. Goldie, W. Haemolytic streptococcus in aetiology of rheumatic fever and rheumatoid arthritis. *Lancet* **2**:246-249, 1938.
46. Collis, W. R. F., Sheldon, W., and Hill, N. G. Cutaneous reactions in acute rheumatism. *Quart. J. Med.* **1**:511-525, 1932.
47. Gibson, H. J., and McGibbon, J. P. Allergic skin reaction after scarlet fever. *Lancet* **2**:729-731, 1932.
48. Wilson, M. G., Schweitzer, M. D., and Lubschez, R. Familial epidemiology of rheumatic fever: genetic and epidemiologic studies: genetic studies. *J. Pediat.* **22**:468, 1943.
49. Klinge, F. Der Rheumatismus: pathologisch-anatomische und experimentell-pathologische Tatsachen und ihre Auswertung für das ärztliche Rhenomaproblem. *Ergebn. d. allg. Path. u. path. Anat.* **27**:1-351, 1933.
50. Murphy, G. E., and Swift, H. F. Induction of rheumatic-like cardiac lesions in rabbits by repeated focal infections with group A streptococci: comparison with cardiac lesions of serum disease. *J. Exper. Med.* **91**:485-498, 1950.
51. Rantz, L. A., Boisvert, P. J., and Spink, W. W. Etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.* **76**:131-138, 1945.
52. Miller, J. M., Kebrick, S., and Massell, B. F. Antibody response to non-streptococcal antigens as related to rheumatic fever susceptibility. *J. Clin. Investigation* **32**:691-695, 1953.
53. Quinn, R. W., Seastone, C. V., and Dickie, H. A. Antibody production and tuberculin sensitivity in individuals with history of rheumatic fever. *J. Immunol.* **70**:493-495, 1953.
54. Denny, F. W., Jr. Prophylaxis of streptococcal infections. In *Streptococcal Infections.* Edited by M. McCarty. 218 pp. New York: Columbia University Press, 1954. Pp. 176-196.
55. Massell, B. F., et al. Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococci respiratory infections: progress report. *J.A.M.A.* **146**:1469-1474, 1951.
56. Billings, F. Chronic focal infection as causative factor in chronic arthritis. *J.A.M.A.* **61**:819-822, 1913.
57. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J. Bacteriology of blood and joints in chronic infectious arthritis. *Ann. Int. Med.* **43**:571-605, 1929.
58. Gray, J. W., and Gowen, C. H. Role of streptococcus in arthritis deformans: improved cultural method. *Am. J. M. Sc.* **182**:682-700, 1931.
59. Margolis, H. M., and Dorsey, A. H. E. Bacteriology of blood in chronic infectious arthritis. *J. Infect. Dis.* **46**:442-459, 1930.
60. *Idem.* Chronic arthritis: bacteriology of affected tissues. *Arch. Int. Med.* **46**:121-136, 1930.
61. Collins, D. H. Pathology of synovial effusions. *J. Path. & Bact.* **42**:113-140, 1936.
62. Blair, J. E., and Hallman, F. A. Rheumatoid (atrophic) arthritis: bacteriologic cultures of synovial fluid and of tissues. *Arch. Int. Med.* **53**:87-96, 1934.
63. Angevine, D. M., Rothbard, S., and Cecil, R. L. Cultural studies on rheumatoid arthritis and rheumatic fever. *Ann. Rheumatic Dis.* **3**:101-106, 1942.
64. Sabin, A. B. Mice as carriers of pathogenic pleuropneumonia-like microorganisms. *Science* **90**:18, 1939.
65. Preston, W. S. Arthritis in rats caused by pleuropneumonia-like micro-organisms and relationships of similar organisms to human rheumatism. *J. Infect. Dis.* **70**:180-184, 1942.
66. Okell, C. C., and Elliott, S. D. Bacteriaemia and oral sepsis, with special reference to aetiology of subacute endocarditis. *Lancet* **2**:869-872, 1935.
67. Glaser, R. J., Dankner, A., Mathes, S. B., and Harford, C. G. Effect of penicillin on bacteremia following dental extraction. *Am. J. Med.* **4**:55-65, 1948.
68. Dawson, M. H., and Olmstead, M. Antistreptolysin titers in rheumatoid arthritis. *Proc. Soc. Exper. Biol. & Med.* **34**:82-84, 1936. Agglutination and precipitation reactions in rheumatoid arthritis with hemolytic streptococci, groups A to G. *Ibid.* **34**: 80-82, 1936.
69. Cecil, R. L., and deGara, P. F. Agglutination reaction for hemolytic streptococci in rheumatoid arthritis: its significance in diagnosis and treatment. *Am. J. M. Sc.* **211**:472-479, 1946.
70. Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. *Proc. Soc. Exper. Biol. & Med.* **68**:1-6, 1948.
71. Favour, C. B., Janeway, C. A., Gibson, J. G., II, and Levine, S. A. Progress in treatment of subacute bacterial endocarditis. *New Eng. J. Med.* **234**:71-77, 1946.
72a. Dawson, M. H., Olmstead, M., and Boots, R. H. Agglutination reactions in rheumatoid arthritis. I. Agglutination reactions with Streptococcus hemolyticus. *J. Immunol.* **23**:187-204, 1932.
72b. Howe, C., Miller, E. S., Kelly, E. H., Bookwalter, H. L., and Ellingson, H. V. Acute brucellosis among laboratory workers. *New Eng. J. Med.* **236**:741-747, 1947.
72c. Spink, W. W., Hall, W. H., Shaffer, J. M., and Braude, A. I. Human brucellosis: its specific treatment with combination of streptomycin and sulfadiazine. *J.A.M.A.* **136**:382-387, 1948.
73. Rich, A. *Pathogenesis of Tuberculosis.* Second edition. 1028 pp. Springfield, Illinois: Thomas, 1951. P. 448.
74. Wells, A. Q., and Wylie, J. A. H. Tuberculin-neutralizing factor in serum of patients with sarcoidosis. *Lancet* **1**:439-441, 1949.
75. Long, J. B., and Favour, C. B. Ability of ACTH and cortisone to alter delayed-type bacterial hypersensitivity. *Bull. Johns Hopkins Hosp.* **87**:186-202, 1950.
76. Dawson, M. H., Olmstead, M., and Boots, R. H. Agglutination reactions in rheumatoid arthritis. II. Nature and significance of agglutination reactions with Streptococcus hemolyticus. *J. Immunol.* **23**:205-228, 1932.
77. Swift, H. Streptococci. In *Bacterial and Mycotic Infections of Man.* Edited by R. J. Dubos. 785 pp. Philadelphia: Lippincott, 1948. P. 237.
78. Favour, C. B., and Sosman, M. C. Erythema nodosum. *Arch. Int. Med.* **80**:435-453, 1947.
79. Favour, C. B. Manifestation of bacterial allergy in eye: study of 35 cases referred to internist for search for foci of infection. *Am. J. Ophth.* **40**:705-723, 1955.
80. Cecil, R. L., and Angevine, D. M. Clinical and experimental observations on focal infection with analysis of 200 cases of rheumatoid arthritis. *Ann. Int. Med.* **12**:577-584, 1938.
81. Möllgard, H. *Chemotherapy of Tuberculosis: Experimental foundation and preliminary clinical results.* 419 pp. Copenhagen: A. Busck, 1924.
82. Feldt, A. Chemo- und Serumtherapie Pneumokokken-Infektion: Chemotherapeutische-Versuche mit Gold. *Deutsche med. Wchnschr.* **61**:593-595, 1935.
83. Collier, W. A., and Verhoog, M. J. Die Wirkung von Auro-Detoxin und Auro-Detoxin Typ 70 auf verschiedene Infektionen. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **98**:174-191, 1937.
84. Collier, W. A. Die Beeinflussung der Streptokkeninfektion der weissen Maus durch Gold. *Med. Klin.* **29**:1447-1449, 1933.
85. Dawson, M. H., and Hobby, G. L. Chemotherapy of experimental hemolytic streptococcal infections with gold salts. *J. Pharmacol. & Exper. Therap.* **69**:359-364, 1940.
86. Sabin, A. B., and Warren, J. Curative effect of certain gold compounds on experimental, proliferative, chronic arthritis in mice. *J. Bact.* **40**:825-856, 1940.
87. Heilman, F. R. Chemotherapy in experimental infections caused by Streptobacillus moniliformis. *Science* **91**:366, 1940.
88. Rothbard, S., Angevine, D. M., and Cecil, R. L. Influence of gold sodium thiomalate (myocrysin) on prevention of hemolytic streptococcal arthritis in rats. *J. Pharmacol. & Exper. Therap.* **72**:164-174, 1941.
89. Hench, P. S., et al. Problem of rheumatism and arthritis: review of American and English literature for 1938: sixth rheumatism review. *Ann. Int. Med.* **13**:1837-1990, 1940.
90. Beard, R. L., et al. *Insect Physiology.* Edited by K. D. Roeder. 1100 pp. New York: Wiley, 1953.
91. Snell, G. D. Genetics of transplantation. *J. Nat. Cancer Inst.* **14**:691-704, 1953.
92. Owen, R. D. Immunogenetic consequences of vascular anastomoses between bovine twins. *Science* **102**:400, 1945.
93. Dunsford, I., et al. Human blood-group chimera. *Brit. M. J.* **2**: 81, 1953.
94. Symposium: relation of immunology to tissue homotransplantation. *Ann. New York Acad. Sc.* **59**:277-466, 1955.
95. Favour, C. B. Symposium on agammaglobulinemia: immunology of homotransplantation. *Transplantation Bull.* **2**:81-85, 1955.
96. Good, R. A., and Varco, R. L. Successful homograft of skin in child with agammaglobulinemia. *J.A.M.A.* **157**:713-716, 1955.
97. Lindemann, W. Sur le mode d'action de certains poisons rénaux. *Ann. Inst. Pasteur* **14**:49-59, 1900.
98. Masugi, M. Über die spezifisch zytotoxische Wirkung des Antinieren-und-leberserums sowie über die sog. umgekehrte Anaphylaxie. *Tr. Japanese Path. Soc.* **19**:132-137, 1929.
99. Pressman, D., and Keighley, G. Zone of activity of antibodies as determined by use of radioactive tracers: zone of activity of nephrotoxic antikidney serum. *J. Immunol.* **59**:141-146, 1948.
100. Kay, C. F. Mechanism by which experimental nephritis is produced in rabbits injected with nephrotoxic duck serum. *J. Exper. Med.* **72**:559-572, 1940.
101. Rammelkamp, C. H. Acute hemorrhagic glomerulonephritis. In *Streptococcal Infections.* Edited by M. McCarty. 218 pp. New York: Columbia University Press, 1954. Pp. 197-207.
102. Burky, E. L. Staphylococcus toxin and antitoxin: experimental and clinical studies with special reference to ophthalmology. *Internat. Clin.* (Series 46) **3**:258-289, 1936.
103. Elschnig, A. Studien zur sympathischen Ophthalmie. I. Wirkung von Antigenen vom Augeneinnern aus. *Arch. f. Ophth.* **75**:459-473, 1910. Studien zur sympathischen Ophthalmie. II. Die antigene Wirkung des Augenpigmentes. *Ibid.* **76**:509-546, 1910. Studien zur sympathischen Ophthalmie. IV. Die antigene Wirkung der Augenpigmente. *Ibid.* **79**:428-441, 1911.
104. Woods, A. C. *Allergy and Immunity in Ophthalmology. (Wilmer Ophthalmological Institute, the Johns Hopkins Hospital and University,* Monograph No. 1.) 176 pp. Baltimore: Johns Hopkins Press, 1933.
105. Kabat, E. A., Wolf, A., and Bezer, A. E. Rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants. *J. Exper. Med.* **85**:117-130, 1947.
106. Freund, J., Lipton, M. M., and Thompson, G. E. Impairment of spermatogenesis in rat after cutaneous injection of testicular suspension with complete adjuvants. *Proc. Soc. Exper. Biol. & Med.* **87**:408-411, 1954.
107. Finch, S. C., Ross, J. F., and Ebaugh, F. G., Jr. Immunologic mechanisms of leucocyte abnormalities. *J. Lab. & Clin. Med.* **42**:555-569, 1953.
108. Bedson, S. P. Blood-platelet anti-serum, its specificity and role in experimental production of purpura. *J. Path. & Bact.* **24**: 469-476, 1921.
109. Ackroyd, J. F. Pathogenesis of thrombocytopenic purpura due to hypersensitivity to sedormid (allyl-isopropyl-acetyl-carbamide). *Clin. Sc.* **7**:249-285, 1949.

110. *Idem.* Mechanism of reduction of clot retraction by sedormid in blood of patients who have recovered from sedormid purpura. *Clin. Sc.* **8**:235-261, 1949.
111. *Idem.* Cause of thrombocytopenia in sedormid purpura. *Clin. Sc.* **8**:269-287, 1949.
112. Bedson, S. P. Blood-platelet anti-serum, its specificity and role in experimental production of purpura. *J. Path. & Bact.* **25**: 94-107, 1922.
113. Woodruff, M. F. A., Forman, B., and Fraser, K. B. Effect of antilymphocytic serum on circulating antibody levels. *J. Immunol.* **67**:57-62, 1951.
114. Favour, C. B. Lytic effect of bacterial products on lymphocytes of tuberculous animals. *Proc. Soc. Exper. Biol. & Med.* **65**:269-272, 1947.
115. Boyden, S. V. Fixation of bacterial products by erythrocytes in vivo and by leucocytes. *Nature* (London) **171**:402, 1953.
116. Pascher, F., Borota, A., and Davis, B. Pitfalls in interpretation of L.E. preparation. *J. Invest. Dermat.* **24**:311-322, 1955.
117. McKee, K. T., and Swineford, O., Jr. Homologous tissue sensitization: failure to produce joint and kidney lesions or precipitins with homologous tissue plus Streptococci. *Ann. Rheumat. Dis.* **10**:116, 1951.
118. Glynn, L. E., and Holborow, E. J. Conversion of tissue polysaccharides to auto-antigens by group A beta-haemolytic streptococci. *Lancet* **2**:449-451, 1952.
119. Favour, C. B., Goldthwait, J. C., and Bayles, T. B. Attempt to produce experimental arthritis with synovotoxic antiserum tagged with I^{131}. *Ann. Rheumat. Dis.* **13**:369, 1954.

MEDICAL INTELLIGENCE

ADVANCED PROSTATIC CARCINOMA*

A Study of Ten-Year Survival after Antiandrogenic Treatment

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FOURTEEN years have now elapsed since Huggins and his co-workers[1,2] reported on the treatment of prostatic carcinoma by antiandrogenic methods. Although it has become apparent that orchiectomy or estrogenic hormones or both have failed to cure the disease, it is generally agreed that life is prolonged, pain and suffering are relieved, and the size and consistence of the prostatic neoplasm and often its distant lymphatic, osseous or pulmonic metastases are remarkably influenced in a sufficiently significant percentage of cases to warrant the institution of this treatment in all cases of "advanced" prostatic carcinoma.[3] Certainly, for "early" prostatic carcinoma, an attempt at complete eradication of the disease by radical prostatectomy must be considered to offer the patient the best chance for a five-year or ten-year survival with freedom from disease.[4]

"Early" carcinoma may be defined as the presence of a stony-hard, asymptomatic nodule, discovered usually on routine rectal examination of a male patient, in whom the lesion seems to be confined to the prostate without evidence of extracapsular extension, with no demonstrable bone metastases and with a normal serum acid phosphatase level.[5] This nodule must be shown histologically to be malignant either by needle biopsy through the perineum or by frozen-section biopsy through the open perineum, preliminary to the performance of radical prostatectomy.

In marked contrast with these ideal early lesions is the situation that pertains to the vast majority of prostatic carcinomas encountered in clinical practice. These are advanced lesions having palpable extension beyond the capsule into the seminal vesicles, lateral pelvic walls, bladder neck and often distant hematogenous or lymphogenous metastases. In most clinics this group comprises 90 to 95 per cent of all clinically recognizable prostatic carcinomas. The lesions are too far advanced to allow a reasonable chance of cure by radical prostatectomy. At best, one can hope only for palliation of symptoms and prolongation of life among these unfortunate patients. It is with this group that this study is concerned.

Five-year survival in advanced carcinoma has been reported in a series of 127 patients without bone metastases followed for five years or more, of whom 46.1 per cent survived for five years or longer.[6] The superiority of orchiectomy and estrogen treatment over estrogen alone was also shown in that study.

STUDY

In this study attention was called to ten-year survival in patients with advanced prostatic carcinoma treated by immediate orchiectomy and stilbestrol.

The records of all patients who had bilateral orchiectomy on the Urological Service of the Massachusetts General Hospital between July, 1941, and June, 1945, for advanced prostatic carcinoma were examined. These patients all received estrogenic hormone, usually stilbestrol, 5 mg. daily by mouth. The only other treatment was transurethral resection when indicated for the relief of bladder-neck obstruction.

In all these patients there was no reasonable doubt about the diagnosis. In 84 per cent the diagnosis was confirmed histologically by microscopical examination of tissue removed either by needle biopsy through the perineum or by transurethral resection. In the 16 per cent without histologic confirmation, there was no doubt by the clinical examination and subsequent course of the patient that this disease was present. All the ten-year survivors had positive histologic reports.

In all, the records of 64 patients were reviewed. All but 2 were followed for ten years or more. These 2 were considered in the calculations as having died of prostatic carcinoma before the tenth year. Survival was calculated from the time of performance of

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bilateral orchiectomy and institution of estrogen treatment, not from the time of onset of symptoms.[7]

Results

Eighteen of these patients had demonstrable bone metastases when first seen, and not 1 of them survived for ten years.

Of forty-six patients who had no demonstrable bone metastases when first seen, 5 died of unassociated disease as follows: 2 died of heart disease — 1 eleven months and 1 seven years after orchiectomy; 1 died of oat-cell carcinoma of the lung — three and three-fourths years after orchiectomy; 1 died of a cerebral accident — three years after orchiectomy; and 1 was accidentally killed by a bus a week after orchiectomy. Among the group without bone metastases, 7 patients lived for ten years or longer. Thus, 7 of 41 patients survived for ten years or longer, a percentage of 17.

These patients were generally in good condition for their respective ages and without significant urinary symptoms. In the majority rectal examination showed usually a small, firm, asymmetric prostate in which the diagnosis of residual carcinoma could reasonably be entertained. They often had moderate to marked hypertrophy of the breasts, but in general they were getting along reasonably well. They could not, however, be considered cured and are all assumed to harbor residual neoplastic disease.

Summary and Conclusions

Seventeen per cent of the patients without bone metastases with prostatic carcinoma too extensive for cure by radical prostatectomy will survive for ten years if treated by immediate orchiectomy and stilbestrol and if the bladder-neck obstruction is relieved by transurethral resection — provided the patients survive unassociated disease.

Only 39 per cent of five-year survivors lived for ten years or longer after antiandrogenic treatment in the group without bone metastases.

None of the patients having bone metastases when first treated survived for ten years in this series.

References

1. Huggins, C., and Hodges, C. V. Studies on prostatic cancer. I. Effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of prostate. *Cancer Research* **1**:293-297, 1941.
2. Huggins, C., Stevens, R. E., Jr., and Hodges, C. V. Studies on prostatic cancer: effects of castration on advanced carcinoma of prostate gland. *Arch. Surg.* **43**:209-223, 1941.
3. Nesbit, R. M., and Baum, W. C. Endocrine control of prostatic carcinoma: clinical and statistical survey of 1,818 cases. *J.A.M.A.* **143**:1317-1320, 1950.
4. Young, H. H. Cure of cancer of prostate by radical perineal prostatectomy (prostato-seminal vesiculectomy): history, literature, and statistics of Young's operation. *J. Urol.* **53**:188-252, 1945.
5. Gutman, A. B. Serum "acid" phosphatase in patients with carcinoma of prostate gland: present status. *J.A.M.A.* **128**:1112-1116, 1942.
6. Ganem, E. J. Carcinoma of prostate gland — 5 year survival following antiandrogenic treatment. *J. Urol.* **74**:804-808, 1955.
7. Staubitz, W. J., Oberkircher, O. J., and Lent, M. H. Clinical results of treatment of prostatic carcinoma over ten-year period. *J. Urol.* **72**:939-945, 1954.

DOCTORS AFIELD

Jean-Paul Marat — Physician, Philosopher, Patriot

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JEAN-Paul Mara, a physician and a controversial figure of the French Revolution, was born in Boudry, Neuchâtel, in 1743, son of Jean Paul Mara, who has been described variously as a doctor, a designer of cloth and a master of the Italian and Spanish languages. He added the "t" to his name in later years to give it a French appearance.

Until about 1765, when he went to live in England, little is known of Marat's life. He seems to have studied medicine for two years at the University of Bordeaux and later in Paris and Holland, a period when he made his first venture into literature. This was entitled "The Adventures of the Young Count Potowski," but the book remained unpublished during his lifetime. Details of his first two years in England are as fragmentary as those of his travels on the Continent, but he emerged if not as a young count, at least as a fashionable physician with a large practice, a member of society and a writer of repute. St. Andrew's University in Scotland awarded him the honorary degree of Doctor of Medicine in 1775, on the recommendation of Drs. Hugh James and William Buchan. Not long afterward, Marat published his *Essay on the Human Soul,* and followed it by a more pretentious volume, *A Philosophical Essay on Man.* In these essays he accepted the duality of body and soul, but argued that although there was no direct relation between the two, there were reciprocal relations. Hence these must be due to some third influence, which he termed the "nervous fluids." One might say that Marat was an early student of psychosomatic medicine. Marat then attempted to spread his theories on the Continent, but in France they met with a less favorable reception. In 1774, in an attempt to arouse a sense of civic duty in the citizens of England, he wrote *The Chains of Slavery.* Not unnaturally this work met with little approbation in government circles, but gained popularity for him in patriotic societies of the time. He concluded his literary career in England with two papers in the field of medicine, one *An Essay on the Gleets* and the other *An Inquiry into Nature, Cause and Cure of a Singular Disease of the Eyes.* The singular disease "which may be termed Accidental Presbytopia or Long-sightedness, is ever the fatal consequence of taking prepared Mercury without proper Care." These essays were both published in 1891 by Bailey, the librarian of the Royal College of Surgeons. Many false stories were circu-

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lated about Marat at this time, including those of a criminal record.

In 1777 Marat returned to France and until 1786 held the position of physician to the household of the Count of Artois. At the same time he was permitted to engage in private practice where he enjoyed an increasing prestige and a wealthy clientele. The story

JEAN-PAUL MARAT

was told that one of his patients, regarded by other physicians as hopelessly incurable from tuberculosis, was treated by Marat with an "artificial anti-pulmonic water" and with such success that she believed herself cured. This medication, later analyzed by the doctor-regent of the Faculty of Medicine, was found to be little more than chalk and water. In later years Marat's political enemies were to make capital out of his sale of patent medicines; whether he was a good physician or not, he achieved fame as a specialist on diseases of the lung and of the eye.

From the time he resigned from the service of the Count of Artois until the French Revolution, Marat gave his time to scientific investigation. He wrote works on fire, electricity, light and optics and achieved distinction in France and other countries. The results of some of these studies were first published in a 38-page brochure, which received honorable mention from the French Academy of Sciences, even though that body would not support his theories. This slight, as Marat saw it, was the origin of his life-long squabble with the Academy. If he had been accepted by that institution he might perhaps have lived happily in his prestige as a scientist. Much has been written by early historians to show that Marat was a charlatan, but there is little real evidence of this.

As his scientific work tapered off around 1789, his political activity increased. He edited and published *L'Ami du Peuple,* so colored by his own personality that he became himself known as "Friend of the People." The first regular issue of the journal was in 1789, and, with several lapses, the last number, which he edited under a new title, "Le Publiciste de la République Française," appeared the day after his assassination. In his writings Marat launched attacks against the Assembly of the Commune of Paris. He himself took part in the insurrection of October 5-6, when a march was made to Versailles. On this and other counts, a decree was issued against him; he was forced into hiding and later arrested. However, the Comité des Recherches acquitted him when he explained his attacks away on the grounds of patriotic fervor. Because of his violent denunciation of Lafayette, Necker and others, he fled to England for three months. Marat seemingly foresaw the Revolution, but with no violent change in the monarchy. On September 2, 1792, he became a member of the Comité de Surveillance of the Commune. Though he was not yet an avowed revolutionary, he was a member of the National Convention that made France a republic on September 22, 1792. He became deeply involved in the struggle between the Jacobins (violent radicals) and the Girondins (moderate republicans) and was eventually forced into hiding for the last time. He was finally arrested and called before the Revolutionary Tribunal. The whole of France watched the trial with interest, and on his acquittal, praise and congratulations poured in from all quarters. Marat himself believed that with the overthrow of the Girondins his work in the Convention was over. His influence was beginning to ebb, and physically he was a sick man. He had long suffered from a chronic skin disease, which had been greatly aggravated by frequent hiding in cellars, sewers and other underground places, and he sought relief from itching and pain by immersing himself in a specially designed bath tub in which he not infrequently received callers.

Marat resigned from the Convention on June 3, 1793. His working days were nearing an end, and he was greatly troubled by the internal disorders of his native country. In Normandy, his enemies, the Girondins, were inciting revolt, and from Normandy came Marie-Anne-Charlotte Corday d'Armont. Deploring the ill-treatment of the Girondins in Normandy and eager and willing to become a martyr for liberty, she obtained entry to Marat's home by a subterfuge and stabbed him to death in his famous bath tub. Only fifty years old but one of the oldest prominent figures of the Revolution, a man of paradoxes, a physician who worked without remuneration in the cause of science yet sold patent medicines, he was regarded variously as a martyr of liberty, a national hero, a monstrous creature and a legend of terror. Gibbs, in his *Men and Women of the French Revolution,* gives the following description:

> There has been more violent rhetoric pronounced upon the character of Jean Paul Marat . . . than upon any other man of the Revolution . . . History became fabulous when dealing with his life and work. Plain facts were distorted, and where fact was lacking, invention filled the gap with falsehoods darkly shaded as the rest of the story.

It is revealing that for almost two centuries historical opinion of Marat has swung backward and forward. Some of the violent scorn heaped on him by early historians has at times been cast on those historians themselves by later biographers. Perhaps the truth of the matter lies between these extremes. The Marat of some is a hateful figure, and that of others is patently whitewashed. Gibbs's final characterization offers Marat as "the living type of the French people in revolution, possessed by all the virtues of passion as well as by its vices . . ."

Bibliography

Bax, E. B. *Jean-Paul Marat: The people's friend.* 353 pp. London: Grant Richards, 1900.

Gibbs, P. *Men and Women of the French Revolution.* 390 pp. London: Kegan Paul, Trench & Trübner, 1906.

Gottschalk, L. R. *Jean-Paul Marat: A study in radicalism.* 221 pp. New York: Greenberg, 1927.

Marat, J. P. *1. An Essay on the Gleets. 2. An Inquiry into the Nature, Cause and Cure of a Singular Disease of the Eyes: Reprint of two tracts.* Edited by J. B. Bailey. 45 pp. London: Percival & Co., 1891.

JEAN BAPTISTE CHARCOT

THE article on Dr. Jean Baptiste Charcot in the May 3 issue of the *Journal* calls attention to an unusually brilliant member of the medical profession who made a name for himself largely in the field of exploration. It so happened that Dr. Henry R. Viets, curator of the Boston Medical Library, has had on his desk a medal of Dr. Charcot that was given to him nearly thirty years ago by the explorer. This medal is of more than ordinary interest, for the portrait of Charcot was modelled by Paul Richer, the artist of the Salpêtrière who published many treatises from that hospital when the elder Charcot was at the height of his fame as a neurologist, and who made a series of statuettes representing neurologic diseases.

Jean Baptiste Charcot

Expéditions Polaires Françaises

As the Curator remembers Charcot, the likeness is excellent.

On the reverse of the medal, under the title "Expéditions Polaires Françaises," is a reproduction of the famous vessel designed to Charcot's specifications for the explorations in northern waters mentioned in the article by Captain Joseph A. Gélinas. This is the polar yacht, *Pourquoi Pas?,* that Charcot used for many years in his explorations. The reproduction on the back of the medal appears to be excellent, and presumably the artist, Lindauer, must have drawn it actually from the ship itself or from photographs. In the foreground the rough waters of the Arctic are indicated and in the background an iceberg nearly as high as the masts of the yacht. Both sides of the medal are here reproduced.

CASE RECORDS
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BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 42231

PRESENTATION OF CASE

A twenty-nine-year-old man entered the hospital because of headaches.

Fourteen years previously mild headaches were noted, and the blood pressure was 190 systolic. An extensive investigation at another hospital gave no other findings. There continued to be intermittent hypertension, with a blood pressure as high as 220 systolic eleven years before admission when he was in the Army. During the year before entry severe headaches, which were characterized by either a pounding sensation in the occipital region or a dull feeling in the frontal and parietal regions or both, occurred three or four times weekly. The headaches lasted for several hours and were accompanied by palpitation and marked sweating. They usually occurred during the day but occasionally at night; the patient was able to tell when they were imminent. They frequently occurred when he was not at work, but were not precipitated by emotion or any known factor.

There was no history of renal disease, albuminuria or visual disturbances. An intravenous pyelogram one year previously was allegedly normal. During the year before admission the patient noted increased coldness in the fingers and toes while asleep at night. Seven years before admission a small gastric ulcer was demonstrated in an x-ray examination. A recent upper gastrointestinal series was said to have shown scarring in the region of the previously demonstrated ulcer.

Physical examination showed a moderately obese man in no distress. Striae were noted in the skin over both hips. Ophthalmoscopic examination revealed slight arteriovenous nicking and no hemorrhages or exudates. Examination of the lungs was negative. The left border of cardiac dullness extended 4 cm. beyond the midclavicular line. A Grade 2, systolic murmur was audible along the left sternal border. Good dorsalis-pedis pulsations were present bilaterally.

The temperature was 98.4°F., the pulse 104, and the respirations 16. The blood pressure was 190 systolic, 135 diastolic, in the right arm and 190 systolic, 135 diastolic, in the left and 220 systolic, 150 diastolic, in the right leg and 210 systolic, 125 diastolic, in the left.

The urine gave a + test for albumin. Examination of the blood revealed a hemoglobin of 15.8 gm. per 100 ml. and a white-cell count of 11,800, with 79 per cent neutrophils. The nonprotein nitrogen was 26 mg., and the fasting blood sugar 128 mg. per 100 ml. The glucose tolerance test showed a fasting blood sugar of 148 mg., and 151 mg. 30 minutes, 160 mg. one hour and 156 mg. per 100 ml. two hours after ingestion of the sugar. The basal metabolic rate was +15 per cent. An intravenous pyelogram demonstrated normal renal function. The right ureter in its upper portion was displaced laterally (Fig. 1). X-ray films of the chest demonstrated some fullness of the left ventricular contour; the lungs and ribs were normal. An electrocardiogram revealed a normal rhythm at a rate of 85; the PR interval was 0.16 second; the T waves were upright, with normal amplitude in Leads 1 and 2, and slightly diphasic in Lead 3; the axis was normal; the precordial leads showed upright R and T waves.

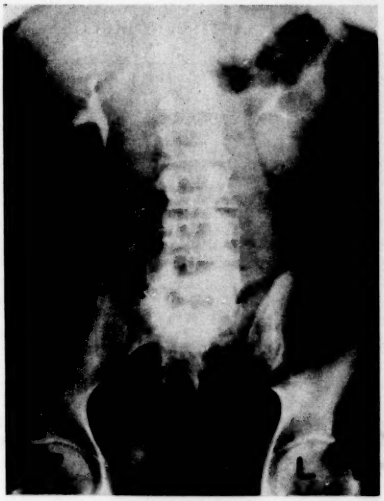

FIGURE 1. *Intravenous Pyelogram, Showing Normal Renal Function.*
The proximal portion of the right ureter is buckled laterally somewhat.

A benzodioxane test showed a fall in blood pressure from 200 systolic, 140 diastolic, to 160 systolic, 100 diastolic. A cold-pressor test revealed a rise in blood pressure from 170 systolic, 110 diastolic, to 190 systolic, 140 diastolic. A test dosage of Regitine resulted in a maximum fall equivalent to 62 mm. of mercury in the systolic pressure and to 42 mm. in the diastolic pressure.

An operation was performed on the sixteenth hospital day.

Differential Diagnosis

Dr. Robert S. Palmer*: When I read this history of a twenty-nine-year-old man with variable paroxysmal hypertension for fourteen years, I thought of pheochromocytoma. Many features suggested it as well as a rumor I had heard after I went off the Service that a patient with a pheochromocytoma had been admitted. There is a wise saying in India that one should never ignore a bazaar rumor. Today, as I walked over to the conference, I saw Dr. Oliver Cope, a well known adrenalectomist. If I do well with this case — as I now fully expect to do — I should receive no credit.

The intermittent hypertension and the type of headaches are characteristic of paroxysmal hypertension caused by a pheochromocytoma. The patient's preknowledge of the headaches is unusual. Except for migraine, most headaches simply appear without warning. The coldness of the fingers and toes is common in either primary hypertension or the hypertension of pheochromocytoma. The basal metabolic rate was not helpful; although we look for an elevated one in pheochromocytoma, it may not be present. The increased rate of the pulse suggests hypermetabolism. An elevated fasting blood sugar curiously accompanies pheochromocytoma. The elevated, especially the flattened, curve of the glucose tolerance test is especially interesting. A benzodioxane test showed a fall in blood pressure. Was the fall maintained?

Dr. Benjamin Castleman: The blood pressure was 190 systolic, 130 diastolic, at 12:03 p.m. when benzodioxane was given; it was 165 systolic, 90 diastolic, at 12:05 p.m. and 180 systolic, 120 diastolic, at 12:06 p.m. The lowered pressure lasted only two minutes.

Dr. Palmer: I do not think that that duration of the lowered blood pressure was long enough to be diagnostic of a pheochromocytoma. How long did the blood pressure remain lowered with the Regitine?

Dr. Evan Calkins: Only for a short time.

Dr. Palmer: I think these particular test results are equivocal and a diagnosis of pheochromocytoma somewhat less likely than I believed when I read the history. Of course, there is a 10 per cent error with the benzodioxane test and a 5 per cent error with the Regitine test.

*Physician, Massachusetts General Hospital.

The extensive investigation fourteen years before admission referred to in the protocol was different from an extensive investigation today. Now there are antiadrenin tests, perirenal and presacral insufflation of air or oxygen and more elaborate tests of kidney function, as well as renal angiograms and renal biopsies. We have learned from the cases of Howard et al.[1] that occasionally unilateral renal disease that causes hypertension may be absolutely undetectable by means other than these tests.

Conspicuous by its absence is the testing of the urinary and blood catechols. In the presence of a pheochromocytoma, these tests may reveal abnormal pressor amines in a very high percentage of cases. When the patient has paroxysmal hypertension, however, provocative substances or maneuvers must be employed for one to be sure that the pressor amines are circulating before the tests are done.

The presence of good dorsalis-pedis pulsations in the legs probably rules out coarctation of the aorta as the cause of the hypertension.

One clinical finding that attracted my attention was the striae in the skin over both hips. The patient was said to have been moderately obese, but nothing was recorded about weight loss or gain. In fact all too little about his appearance and general endocrine status was included. Had he changed in weight?

Dr. Calkins: He had gained weight before admission.

Dr. Palmer: In considering this case I remembered Albright's[2] number-one apothegm in his paper on osteoporosis — namely, the adrenal gland is involved in some way in every disease. I think it is especially involved in the disease or condition called essential hypertension. In considering this case I said to myself, even when the adrenal gland itself has a disease, there is the usual adrenal factor in the pathologic picture. I mean that a pheochromocytoma causes its manifestations by affecting the hypothalamus, which affects the pituitary gland, which in turn affects the adrenal cortex. Albright[3] originally suggested that three classes of hormones (sugar, mineral and nitrogen retaining or androgenic) were secreted from the adrenal cortex. Since then numerous particular substances belonging in these three classes have been identified. Separate cortical hormones have different effects. Some pheochromocytomas, as well as other tumors of the adrenal cortex or medulla, may be inactive and have no pressor or other effect. The medullary tumor, which I assume to have been present in this case, was active. My question is whether or not there was, in addition, tumor, hypertrophy or hyperactivity of the cortex — that is, Cushing's syndrome. Did the striae suggest Cushing's disease? Were they bluish and of considerable extent about the hips? Did the patient have a feminine habitus, and could he represent the rare condition of feminization of the male by adrenocortical disturbance as a result of cancer?

DR. CALKINS: He did not have a feminine habitus. The striae were purplish and occurred about the hips. There was some fullness of the neck.

DR. PALMER: Did the hairline recede?

DR. CALKINS: The beard and hair distribution were normal.

DR. PALMER: A few men with Cushing's syndrome have a feminine habitus. In such patients feminizing hormones are secreted from the adrenal cortex. I wondered if that played a part in the glucose tolerance curve — a high blood sugar, with flattening of the curve. This is pure speculation. We know that in Cushing's syndrome — or in hypertrophy of the adrenal cortex from long stimulation by the hypothalamus or pituitary body — no change in the adrenal cortex may be recognizable either by a competent surgeon at operation or by a competent pathologist. Of course, hyperplasia, without tumor, of the adrenal cortex may produce a Cushing syndrome. The real problem that the physicians had to decide was whether the patient should be operated on. I believe that almost the only good reason for doing a sympathectomy, at least the best reason, is to view the adrenal glands. I appreciate that other people have a different opinion. When there is a serious suspicion of pheochromocytoma, which probably occurs only in about 1 out of 30,000 cases, since the condition is curable, one has to operate. I am not sure, and many other physicians are not sure, that operation helps Cushing's disease unless there is a tumor. If one thought that there was a possibility of a tumor other than, or in addition to, a pheochromocytoma, should other studies have been done? Perhaps they were done and are not yet reported. Presacral oxygen insufflation might demonstrate a tumor although the tumors are often very small. Perhaps additional endocrine studies were done to eliminate the possibility of Cushing's syndrome.

The patient may have had extremely variable essential hypertension. Because of the symptoms and because he had a deformity in the first portion of the duodenum, I wondered about carcinoid and the effect of serotonin, but I do not take this possibility seriously.

I shall say that he had a pheochromocytoma, although it seems a little less likely than before I heard the results of the benzodioxane and Regitine tests. Other disease of the adrenal cortex — hypertrophy, tumor or merely hyperfunction — should be considered. The diagnosis can only be made by inspection of the adrenal glands. Were the urinary or blood catechols determined?

DR. CHARLES H. DUTOIT: Yes; there was repeatedly from 1.5 to 2.5 mg. of nor-epinephrine in twenty-four-hour urinary specimens. There was no detectable amount of epinephrine. The blood level, determined by Dr. Madan Singh, gave a result of 18 microgm. per liter of catechol that appeared to be exclusively nor-epinephrine.

DR. PALMER: That would be abnormal; one would expect that this would have been much lower in the normal patient.

DR. DUTOIT: I was much more impressed by the urinary levels. We have found increased blood levels in patients who do not have pheochromocytomas.

DR. PALMER: The increased catechols in the blood increase the chances to perhaps better than 95 per cent that this patient did have a pheochromocytoma. I shall say that I am considering some additional disease of the adrenal cortex and that in any case it was overactive by reason of the pheochromocytoma that was present.

DR. JOHN DENOVIAN: I should like to comment on Dr. Palmer's figures on the percentage of false-positive tests. The benzodioxane test is much more reliable than he has stated; it is probably closer to 99 per cent; whereas the Regitine test in our series has been falsely positive in as high as 25 per cent of the cases.

DR. CASTLEMAN: Dr. Wang, will you show us the x-ray films?

DR. C. C. WANG: A laminagram of the adrenal regions shows the kidneys in a normal position and no abnormal soft-tissue masses. The intravenous pyelogram demonstrates good renal function bilaterally. In comparison to the left, the upper portion of the right ureter is deviated laterally, suggesting some abnormality. The bladder is not unusual.

DR. PALMER: Perhaps Dr. Calkins will tell us whether presacral insufflation was done, or if not, why it was not done.

DR. CALKINS: I am not aware of any patient who has been tested in that way here. At other hospitals where I have worked, some difficulty arose with the test so that I was not enthusiastic about trying it. I think that in retrospect it would have been advisable if the procedure could have been done without hazard to the patient. I agree with Dr. Palmer about the benzodioxane test. I think the duration of the depressed level of the blood pressure is important. These tests were suggestive but not diagnostic of pheochromocytoma. The over-all picture was that of a pheochromocytoma, and we made that diagnosis on clinical grounds, supported by Dr. DuToit's observations.

DR. OLIVER COPE: The reason we did not consider air insufflation is that the Department of Radiology can delineate adrenal lesions as well or better in a properly prepared patient by the regular films. In these films there are shadows above the kidneys on either side; there is no space for a sizable adrenal tumor between the top of the kidney and the dome of the diaphragm. If a tumor is present it would have to be so small that air insufflation would not have shown it either.

DR. PALMER: What is the risk of air insufflation?

DR. COPE: Of more than 180 cases of air insufflation, we have had no mortality but have had an occasional undesirable complication.

DR. PALMER: Presacral insufflation?

DR. COPE: No; the air was put in the perirenal fascia well below the lower pole of the kidney. The Department of Radiology has missed these tumors only twice; in those cases the tumors were on the right beneath the shadow of the liver, which makes them difficult to find — air or no air. I joined in the diagnosis of mild Cushing's disease preoperatively.

CLINICAL DIAGNOSIS

Pheochromocytoma.

DR. ROBERT S. PALMER'S DIAGNOSIS

Pheochromocytoma.
? Complicating Cushing's syndrome.

ANATOMICAL DIAGNOSES

Pheochromocytoma, retroperitoneal, right (extra-adrenal).
Adrenocortical hyperplasia, mild.

PATHOLOGICAL DISCUSSION

DR. COPE: In this patient we made a right-sided incision from which it was possible to palpate the left adrenal gland, which felt normal. We looked at the right adrenal gland, which also appeared normal although it could have been hyperplastic. The right kidney contained no tumor, but a mass that felt like a horseshoe kidney ran across between the lower pole of the kidneys and undoubtedly accounted for the distortion of the ureter on that side. It lay in front of the aorta and behind the vena cava.

Following the policy of dividing the venous return to reduce the expression of the nor-epinephrine before manipulating the tumor, we started on the right side and rolled the vena cava off it, tying off about fifteen small venous tributaries that emptied directly into the vena cava. The mass was large and irregular. The mass so involved the vena cava that I was before long in the vena cava and the left renal vein, through the back of both. The tumor had grown up over the right renal artery, which was barely detectable in the dome of the tumor. It looked as though we were going to have to sacrifice the right or the left kidney to do a subtotal resection of the tumor. By this time there was a large gap in the vena cava, and in spite of its being blocked off below with a clamp, the patient had lost a considerable amount of blood. We abandoned the idea of removing the tumor, knowing that we were going to be in trouble with the kidney. Moreover, the patient was in extremis, with no blood pressure. Dr. Calkins was managing him with the Anesthesia Department during the entire procedure. The blood pressure went sky high to begin with and then went shuttling down.

DR. CALKINS: During the early part of the operation the blood pressure settled down to a level of about 160 systolic, 100 diastolic, but the pulse rate was extremely rapid. We debated many times about using an epinephrine competitor such as Regitine but did not do so because the blood pressure seemed to be at a fairly satisfactory level. At the last stage of operation the blood pressure became unobtainable. Although it initially responded well to nor-epinephrine, we were unable to restore it to its preoperative levels, or to obtain any flow of urine despite large doses of this drug. The situation was doubly difficult because we could not be absolutely certain whether pharmacologically the tumor was in or out. The patient died twelve hours after the conclusion of the operation.

DR. CASTLEMAN: The tumor, which measured 11 by 8 by 8 cm. and weighed approximately 200 gm., was hemorrhagic and lay behind the vena cava and anterior to the aorta (Fig. 2). It could be separated from the vena cava but was quite adherent to it. It extended from the level of the celiac axis to 3 cm. above the bifurcation of the aorta. The right renal artery extended along the posterior aspect of the tumor and had produced a groove in the tumor. The cut surface of the tumor was very necrotic, yellowish and hemorrhagic. The tumor received its blood supply from the adrenal, renal and three lumbar arteries on the right side. Microscopical examination of the tumor showed that it was a characteristic pheochromocytoma. There was no evidence of malignant change. The liver was very fatty and, in addition, showed a tremendous amount of congestion.

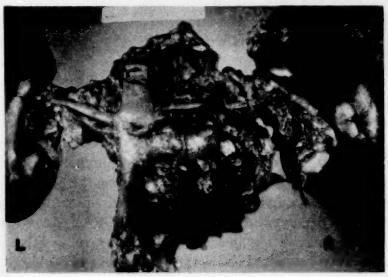

FIGURE 2. *Posterior View of the Retroperitoneal Pheochromocytoma.*

Another finding of interest was marked sclerosis of the left coronary artery in this young man. Of course, he had been exposed to hypertension for some time, but the arterioles of the kidneys were almost perfectly normal. I think that in more than half the cases of pheochromocytoma, arterioles in the kidneys are normal. The Mayo Clinic[4] reported 15 cases, of which 9 had normal arterioles in the kidneys.

DR. PALMER: Was the adrenal cortex normal?

DR. CASTLEMAN: I was coming to that, Dr. Palmer. The adrenal glands were heavier than normal: one weighed 10 gm., and the other weighed 11 gm. Nor-

mally, together, they should weigh about 12 gm. The cortex was somewhat hyperplastic but contained no true nodules; Dr. Richard B. Cohen thought that there was early nodularity, which may well have been associated with some Cushingoid effect.

The heart was hypertrophied, weighing 570 gm.

DR. DUTORR: Sixteen and a half grams of homogeneous tumor tissue was analyzed for epinephrine and nor-epinephrine. The method used is a combination of several earlier methods. It is based primarily on the method of Von Euler.[5] Per gram of wet tissue we extracted 108 microgm. of nor-epinephrine and 4 microgm. of epinephrine. The concentrations were somewhat lower than tumors assayed by Goldenberg et al.[6] However, they were many times the concentrations in the body fluids and hence probably indicative of a functioning tumor.

REFERENCES

1. Howard, J. E., Berthrong, M., Gould, D. M., and Yendt, E. R. Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. *Bull. Johns Hopkins Hosp.* **94**:51-85, 1954.
2. Albright, F. Osteoporosis. *Ann. Int. Med.* **27**:681-882, 1947.
3. *Idem.* Cushing's syndrome: its pathological physiology, its relationship to adreno-genital syndrome and its connection with problem of reaction of body to injurious agents ("alarm reaction" of Selye). *Harvey Lect.* (1942-1943) **38**:123-186, 1943.
4. Minno, A. M., Bennett, W. A., and Kvale, W. F. Pheochromocytoma: study of 15 cases diagnosed at autopsy. *New Eng. J. Med.* **251**:959-965, 1954.
5. Von Euler, U. S. Fluorimetric micro-method for differential estimation of adrenaline and nor-adrenaline. *Acta physiol. Scandinav.* **33**(Supp. 118):45-56, 1955.
6. Goldenberg, M., Serlin, I., Edwards, T., and Rapport, M. M. Chemical screening methods for diagnosis of pheochromocytoma. I. Nor-epinephrine and epinephrine in human urine. *Am. J. Med.* **16**: 310-327, 1954.

CASE 42232

PRESENTATION OF CASE

A thirty-five-year-old Negro entered the hospital because of dyspnea.

One year previously he noted a persistent dry cough, fatigue, dyspnea on exertion and a feeling of inability to take a deep breath. During the next few months he coughed up blood-tinged sputum, and there were temperature elevations to 104°F. An x-ray film of the chest was said to have been "positive," and he was admitted to another hospital, where Aureomycin was given for "pneumonia." After three weeks he was discharged, but shortly afterward was readmitted to the other hospital because of increasing symptoms. Numerous examinations for acid-fast bacilli were negative. With Aureomycin therapy he gradually improved and remained almost totally asymptomatic until two months before entry. During the two months before admission he noted marked fatigue, temperature elevations to 102°F., night sweats, shaking chills, anorexia, increased dyspnea on exertion, a cough productive of white, mucoid sputum with intermittent hemoptyses consisting of up to 50 ml. of dark-red sputum and a weight loss of 5 to 10 pounds. There was no history of exposure to tuberculosis or beryllium.

Twelve years before admission there was an episode of "tonsillitis" for two months, with enlarged tonsils, sore throat, high fever and swelling of the left side of the neck. Since then he had from time to time been aware of an enlarged lymph node in the right axilla that was occasionally tender. A tonsillectomy was allegedly performed ten years before entry. He had worked as a welder for three years thirteen years before admission and in a paper packing factory for ten years before entry.

Physical examination revealed a well-nourished, muscular, healthy-appearing man. The throat was normal. Axillary and supraclavicular lymph nodes measuring several millimeters in diameter and hard inguinal and femoral lymph nodes measuring 1 or 2 cm. in diameter were noted bilaterally. Examination of the chest showed diffuse loud expiratory rhonchi, with prolonged wheezes. The left border of cardiac dullness extended 8 cm. from the midsternal line. The pulmonic second sound was split and greater than the aortic. A Grade 2, soft, systolic blow was audible at the apex. Examination of the abdomen was negative. One observer noted early clubbing of the extremities.

The temperature was 99°F., the pulse 85, and the respirations 18. The blood pressure was 135 systolic, 75 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 12.4 gm. per 100 ml. and a white-cell count of 6900. The sedimentation rate was 45 mm. per hour. The nonprotein nitrogen was 20 mg., the bilirubin 0.3 mg., the total protein 6.8 gm., the albumin 3.9 gm., and the globulin 2.9 gm. per 100 ml. The alkaline phosphatase was 2.9 units. Cephalin flocculation was + in forty-eight hours. The prothrombin content was 83 per cent. Bromsulfalein retention was 1 per cent. The blood Hinton test was negative. Examinations of the sputum for malignant cells were unsatisfactory because of blood, and doubtful. PPD tuberculin skin tests (first and second strength) were negative. X-ray films of the chest demonstrated increased pulmonary bronchovascular markings and patchy consolidation in the left-lower-lung field, enlargement of the hilar shadows bilaterally and enlargement of the upper mediastinum; the heart was not enlarged. A bronchogram showed no abnormality of the proximal bronchi of the upper lobes; examination of the lower lobes showed no definite areas of bronchiectasis; no contrast material was visualized in any portion of the lateral segment of the right middle lobe; some narrowing of the right-middle-lobe bronchus in the area of the expected origin of the lateral segmental bronchus, with evidence of extrinsic pressure on its superior aspect, was noted (Fig. 1). An electrocardiogram showed a nor-

mal sinus rhythm at a rate of 75; the PR and QRS intervals were 0.16 and 0.08 second, respectively; the axis was +80 to 90°; the T waves were inverted in Leads V_1 through V_3, V_2R and V_4R; there was a small R wave and predominant S wave in Leads V_3R and V_4R.

Bronchoscopic examination showed widening and partial fixation of the carina, bleeding from the orifice of the right-upper-lobe bronchus, some obstruction of the orifice of the right-middle-lobe bronchus by what looked like inflammatory tissue and narrowing of the bronchi of both lower lobes; a smear taken from the right main bronchus was negative for acid-fast bacilli, and cytologic examination of washings from the bronchus of the right lower lobe for malignant cells was unsatisfactory.

On the third hospital day an operation was performed.

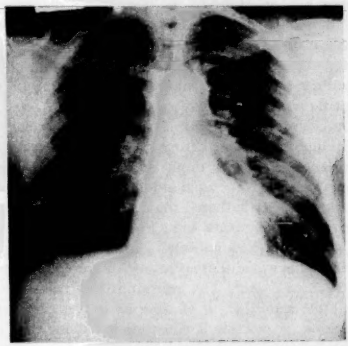

FIGURE 1. *Posteroanterior Roentgenogram of the Chest, Showing Unidentified Linear Markings Bilaterally, with Patchy Consolidation of the Left Lower Lobe.*

DIFFERENTIAL DIAGNOSIS

DR. THOMAS GEPHART*: This relatively young Negro had dyspnea on exertion, tightness in the chest, dry cough, fatigue, mucoid, blood-stained sputum, intermittent rises in temperature to 104°F. and an elevated sedimentation rate. These symptoms first occurred a year before the present episode and apparently responded slowly to Aureomycin. On physical examination the patient appeared well and showed only some questionable clubbing. What diseases come to mind in connection with this type of picture? I think I can rule out the usual bacterial and viral types of pneumonia, for I assume that this was one disease covering at least a year. This conclusion is supported in part by the slow response to Aureomycin.

*Assistant surgeon, Massachusetts General Hospital.

The more chronic types of disease could be grouped as follows: tuberculosis or sarcoidosis; parasitic disease; infection and fibrosis secondary to inhalation of some foreign material; a chronic infection by actinomycosis, yeast or fungus; and neoplastic disease involving the bronchi, particularly on the right side. Before discussing these may we look at the x-ray films?

DR. C. C. WANG: The films of the chest show a considerable increase in the pulmonary markings in both lung fields that is particularly pronounced in the left lower lobe. The hilar shadows appear somewhat fuller than usual, but I cannot delineate any discrete, sharply defined lymph nodes. The upper mediastinum is definitely somewhat widened, probably as a result of enlarged lymph nodes (Fig. 1). Barium-swallow examination shows no intrinsic disease in the esophagus. A bronchogram of the chest gives no definite evidence of bronchiectasis. At the point where the middle-lobe bronchus branches off, there appears to be an extrinsic pressure defect on the superior aspect of the middle-lobe bronchus; the lateral segment of the middle lobe is not filled with contrast material, but there is no evidence of bronchiectasis in that lobe. The heart shadow is not unusual. There is no evidence of bone destruction, and the size of the spleen appears normal.

DR. GEPHART: In a thirty-five-year-old Negro with fever and pneumonitis persisting over a long period, one, of course, thinks of tuberculosis. The findings in the x-ray films, the repeated negative examinations of the sputum for acid-fast bacilli and the negative skin tests make me believe that this was not the diagnosis. I do not believe he had the changes that one would expect with sarcoidosis throughout the lung, although the enlarged lymph nodes would be consistent with it. My opinion is that the failure of the lateral segment of the right-middle-lobe bronchus to fill was the result of pressure on the bronchus, presumably from an enlarged lymph node.

The possibility of parasitic disease such as flatworm or roundworm infection is unlikely in view of the absence of other symptoms; however, both these conditions cause reactions of this type in the lungs.

I know very little about his activity, about his travels and about where he had lived. I think these bear some relation to the discussion, for the condition may have been secondary to his occupation, to the inhalation of foreign material or, of course, to infection with fungus or yeast. We are told that he was not exposed to beryllium — a necessary condition for the diagnosis of berylliosis. There is no information that he was exposed to silicon or talc. His working for ten years in a paper packing factory may have exposed him to string or packing material, such as asbestos, which may have led to a chronic pulmonary reaction with dyspnea and particular susceptibility to secondary infection.

Of the remaining two conditions I shall discuss the malignant processes first, although the age of thirty-five years makes this diagnosis unlikely but does not exclude it. There is no information about whether he was a heavy smoker or not. Of the neoplastic diseases the more likely are alveolar-cell carcinoma and pulmonary adenomatosis. Several features of the history fit into that. The diagnosis is often not made initially. The first sign may be a patchy pneumonitis associated with fever rather than the typical discrete lesion of the other types of malignant tumor. Frequently there is a mucoid sputum, which may not be bloody. There may be an inflammatory appearance of the major bronchi of the lung on bronchoscopy, and the process may be bilateral. In support of this there was a doubtful and also an unsatisfactory cytologic examination of the sputum.

I think that a chronic infection secondary to a yeast or fungous infestation is the more likely cause of this man's difficulty. Had he lived all his life in New England or had he come from the South or traveled abroad?

DR. BENJAMIN CASTLEMAN: I believe that he lived all his life in New England.

DR. GEPHART: Had he ever been in the service?

DR. CASTLEMAN: Yes.

DR. GEPHART: He had been in the service and probably was not fortunate enough to be stationed near his home in New England all the time. For the purpose of discussion I shall assume that he had traveled about the country. The fungous infections that commonly affect the lung include histoplasmosis. This is thought to be endemic in the central Mississippi valley, but cases are being reported along the St. Lawrence valley and in New England. There are two types, the localized and the disseminated. The symptoms may be extremely mild, and as a matter of fact most cases are not picked up clinically. The disease in both its localized and its disseminated form presents symptoms similar to those of tuberculosis. Commonly, in the disseminated type, there is patchy involvement of the lung parenchyma and usually a marked enlargement of the lymph nodes, which later on may calcify. About 170 cases from 12 epidemics of histoplasmosis have been reported.[1] The epidemic type of histoplasmosis is characterized by high fever, with a temperature from 102 to 105°F., and pulmonary symptoms such as cough, chest pain, malaise, fever and so on, which may appear intermittently for one or more years. The diagnosis probably could have been established by means of a skin test or complement-fixation test. There is no information about either of these.

Another possibility is blastomycosis. This usually produces definite lesions, with cavitation and, frequently, skin lesions. One thinks also of actinomycosis that is often of long standing and may produce sputum, which on examination may or may not show sulfur granules. About 80 per cent of the cases that continue for a year or more tend to exhibit cutaneous fistulas or involvement of other organs so that I think this is less likely.

If this man had traveled through the Southwest he could well have had coccidioidomycosis. Usually, this disease is localized. It is recognized clinically in only about 25 per cent of the patients. Only a fraction of these, perhaps 4 or 5 per cent, acquire the disseminated type of disease. In the dark-skinned races, such as the Filipino and Negro, however, the frequency of disseminated disease is about ten or twenty times as high as in the lighter-skinned races. The symptoms—namely, the cough, pain in the chest, fever, sputum that was sometimes bloody, fatigue and marked enlargement of the hilar and mediastinal lymph nodes — are certainly consistent with coccidioidomycosis. The peripheral lymph nodes were also enlarged. Therefore, although I realize that I am "going out on a limb" by making a diagnosis of coccidioidomycosis in a man who may never have been out of New England, I shall make that my first choice. Pulmonary adenomatosis is my second choice.

A PHYSICIAN: Is hemoptysis uncommon in coccidioidomycosis?

DR. GEPHART: I think it is, if there is no evidence of cavitation. When there is cavitation there may be severe hemoptysis. I think there have been one or two fatal cases of coccidioidomycosis from bleeding from cavities. I gathered that this was blood-stained, mucoid sputum rather than frank bleeding.

DR. AUSTIN L. VICKERY: A case of Friedländer's pneumonitis was discussed at one of these conferences about a year ago.[2] The symptoms had been present about the same length of time as in the case under discussion. I wonder if you thought about that possibility?

DR. GEPHART: I think that is a possibility. All I can say is that there was some type of chronic infection in the lung. I cannot say whether the initial agent was a Friedländer bacillus or a foreign body or a fungus.

A PHYSICIAN: Is lymphoma a possibility?

DR. GEPHART: Yes; I did not go over all the possibilities. It would be unusual for lymphoma alone to produce this amount of sputum and make the symptoms localize to the lung.

DR. EDWARD B. BENEDICT: We did two bronchoscopies on this patient. At the first examination there was so much narrowing from extrinsic pressure that I thought we were dealing with lymphoma. Three weeks later there were papillary projections from the bronchus from which we took a biopsy. I thought from the gross appearance of the papillary projections that we were probably dealing with carcinoma.

DR. CASTLEMAN: Dr. Kranes, have you a diagnosis?

DR. ALFRED KRANES: I should have thought more

seriously about lymphoma than Dr. Gephart did since there were recurring episodes of chills and fever and the evidence of enlarged peripheral, mediastinal and carinal lymph nodes.

DR. GEPHART: Was the patient a smoker?

DR. JOHN H. KNOWLES: No; he was not.

CLINICAL DIAGNOSIS

Pulmonary carcinoma.
? Lymphoma.

DR. THOMAS GEPHART'S DIAGNOSIS

Coccidioidomycosis.
? Pulmonary adenomatosis.

ANATOMICAL DIAGNOSIS

Sarcoidosis of bronchus and lymph nodes.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The biopsy that was removed at bronchoscopy and the biopsy of an axillary lymph node done at the same time showed microscopically granulomas with giant cells, which were quite characteristic of sarcoidosis. In some areas we found Schaumann bodies. Sarcoidosis very rarely extends through the wall of the bronchus to involve the bronchial mucosa, but this was one of the exceptions.

This patient was studied carefully by Dr. Knowles, who might have a comment.

DR. KNOWLES: Although there was evidence of a local pathologic process in the lung as manifested by hemoptysis and the right-middle-lobe findings, the fact that struck us was that the patient complained of dyspnea, which invariably indicates a diffuse, widespread pulmonary involvement in chronic disease. From examination of the chest film, although bilateral parenchymal disease was evident, it seemed so minimal that one would not have expected dyspnea. This brings up the important principle that it is the localization of the disease in the pulmonary tree and not necessarily its extent as seen on the x-ray film that determines the degree of functional incapacity. This patient demonstrated by tests of pulmonary function a moderately severe obstructive ventilatory defect as seen in asthma-emphysema states. This indicated to us that, although the lesions were minimal as seen in the x-ray films, they were crucially placed to obstruct air flow at the level of the respiratory bronchiole. Several other patterns of pulmonary dysfunction have been described in pulmonary sarcoidosis, again depending on the area of localization of the disease: there may be extensive involvement noted in the x-ray films, with few or no respiratory symptoms. This form is usually localized to the intra-alveolar area, and moderate reduction in lung volume may result. There may be extensive involvement of the interstitial tissues, resulting in the so-called alveolar-capillary diffusion-block syndrome with its characteristic clinical and physiologic abnormalities. The emphysema state may be produced, as mentioned above, by localization at the level of the respiratory bronchiole and there can be, of course, combinations of the distinct syndromes enumerated above.

Dr. Monroe has been following the patient in the Medical Clinic and has been treating him with Meticorten.

DR. J. THADEUS MONROE, JR.: He has been quite well and was able to return to work. He has had much less dyspnea, no cough and no hemoptysis. The lymph nodes have regressed in size.

DR. CASTLEMAN: Dr. Benedict, is this the second or the third case in which you have been able to make the diagnosis by means of the bronchoscope?

DR. BENEDICT: It is the second. You and I reported a case of sarcoidosis of the bronchus in a twenty-year-old Negress fifteen years ago.[3] In that case there was extensive bullous formation in the bronchial tree, and she was much better after aspiration of secretions and the taking of several biopsies. She had a spontaneous remission.

DR. REED HARWOOD: Is the high fever characteristic of this disease, or is that the result of infection superimposed on the sarcoidosis?

DR. KNOWLES: Fever, particularly high, swinging fever, is unusual in sarcoidosis and in this patient probably indicated secondary infection. Control of the infectious element has done much to alleviate the patient's symptoms by reducing the bronchospasm associated with bronchitis — just as much as the Meticorten.

DR. RICHARD B. COHEN: Dr. Knowles, do you advise using the skin test for sarcoidosis?

DR. KNOWLES: The test is not used in this hospital any longer. It is a long-drawn-out procedure, and after several months of waiting the result may be only a nonspecific granuloma. There are much quicker and more definitive ways of establishing the diagnosis.

REFERENCES

1. Henshaw, H. C., and Garland, L. H. *Diseases of the Chest.* 727 pp. Philadelphia: Saunders, 1956. P. 625.
2. Case Records of Massachusetts General Hospital (Case 41322). *New Eng. J. Med.* **253**:251-254, 1955.
3. Benedict, E. B., and Castleman, B. Sarcoidosis with bronchial involvement: report of case with bronchoscopic and pathological observations. *New Eng. J. Med.* **224**:186-189, 1941.

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THE SMALL UNIVERSITY

ON December 8, 1955, as previously noted in this column, Tufts University held a convocation at the college in Medford to celebrate its acceptance by the Board of Collegiate Authority of the Commonwealth of Massachusetts as a university. As if for the clarification of this new official university status, the working part of the convocation consisted of four concurrent symposiums in each of which the role of the small university in higher education was discussed, from different strategic angles.

Both the final assumption by Tufts of its status as a university and these efforts to evaluate its role as such are evidence of a mounting general interest in higher education by an ever-increasing number of young people, in a prosperous nation, who are able to avail themselves of it. The fruits of prosperity are spilling over from the cornucopia of industry, with a generosity not unrelated to tax exemptions, into the bursaries at the more exalted levels of learning.

The symposiums considered such subjects as the role of faculty scholarship in the small university, the role of the humanities in the engineering curriculum, the role of religion in the small university and the role of the small university in the recruitment and preparation of teachers. Each was presented by a panel of visiting and local experts reinforced by one or more undergraduate participants from the school or department most concerned.

There seems to be little room for argument regarding the desirability of a faculty of scholars, although faculty scholarship is said to be on the decline; according to the Fund for the Advancement of Education the proportion of doctors of philosophy in American faculties is now only about 40 per cent and may drop to 20 per cent within fifteen years. The pithy characterization of Chaucer's Oxford clerk, as one who would gladly learn and gladly teach, is a bit threadbare but has not yet been outmoded. The aphorism that "productive work involves a certain amount of inactivity also, a certain amount of time for contemplation" reflects the parting advice of Lord Adrian on his retirement last year from the presidency of the Royal Society of London.[1] The growing responsibilities of the academic scholar as well as of the scientist have also increased their administrative work; they must be constantly on guard to see that they have the leisure to survey their problems.

The distinction between a small and a large university is relatively unimportant — that between scholarship and training is important and must be preserved; the small university must not and need not make sacrifices in academic quality.

The role of research as a scholarly adjunct was well phrased by President Keeney, of Brown University, in the statement that research represents the bones of scholarship but is usually communicable, in

its skeletal state, only to workers in the field in which it was produced. These bones, when fleshed, become fully rounded scholarship and may be communicated to any receptive person. The function of interpreting and communicating specialized knowledge outside its field was expressed by Lord Adrian as one of the present duties of the Royal Society; the same function has been assumed by the American Academy of Arts and Sciences.[2] President Keeney also emphasized, as have others, the danger of contract research, which increases the size of a faculty and reduces its opportunity for teaching.

In the field of engineering the distinction between scholarship or general education and mere practical training becomes more obvious, and the problem is more acute. An obstacle in the way of achieving both in the same curriculum is the increasing requirements of technical training. The world is too much with us, and since the days cannot be lengthened, their numbers must be increased. The acknowledged desirability — within a university — of educating as well as training its technologists requires a blending of diversification and concentration, and added years in the university in which to do it.

The ultimate function of the small university was perhaps most ably expressed by Mr. Alan L. Seaburg, a fourth-year student in the Crane Theological School. Regardless of mere size it must maintain those standards in the breadth and quality of its curriculum that youth has come to expect. It must maintain as balanced a faculty in any given field for fifteen as for fifty students. The matter of size pertains to numbers of students and amounts of physical equipment, not to the quality of the instruction available.

References

1. General Article. Lord Adrian on functions of Royal Society. *Brit. M. J.* **2**:1443-1445, 1955.
2. Editorial. Dispersion of natural knowledge. *New Eng. J. Med.* **254**: 581, 1956.

ALPHA OMEGA ALPHA — A HALF CENTURY OF SCHOLARSHIP

Even as Harvard Medical School celebrated last week the fiftieth anniversary of the occupancy of its present spacious quadrangle, the Harvard chapter of Alpha Omega Alpha observed its own half century of dwelling in the same marble halls.

Alpha Omega Alpha, dedicated to the proposition of being "worthy to serve the suffering," had been in existence only four years when its eighth chapter was installed at Harvard under the local presidency of Channing Frothingham, Jr., of the fourth-year class. It had had its beginning in Chicago, at the College of Medicine of the University of Illinois, where it had been founded by Dr. William W. Root. Its establishment was a protest against the rowdyism and boorishness that were too often taken to be characteristic of the medical student of the period; its motive was "the advancement of moral and educational standards both in the medical school and in the profession," and the encouragement of "personal honesty and the spirit of medical research."

Comprising not more than a sixth of any fourth-year class, as prescribed by the constitution, A O A chapters have represented the cream of the student crop, forming, according to Dean Quine, of the parent chapter, "a select band whose constantly increasing influence is helping to bring nearer the day when not only a very few medical schools in this country, as at present, but the larger number of them, shall rival any in the world."

Of later vintage than the Harvard installation, chapters of Alpha Omega Alpha were chartered at Tufts College Medical School in 1940 and at Boston University School of Medicine in 1948, giving to the true scholars of each school the right to wear the cherished key, designed after the fashion of a *manubrium sterni hominis*. Election, according to a history of the fraternity-sorority published in 1940, "represents not only a recognition of accomplishment as a student, but also an insignia [!] of both promise and expectancy of leadership in some phase of medicine after graduation."

One is reminded of the general description of those qualified in its early years for inclusion in the Royal College of Physicians of London as "persons profound, sad and discreet, groundedly learned and deeply studied in physic."

SPRING MEETINGS

In the spring a young man's fancy — if he is a budding investigator in the clinical or related biologic sciences — turns away from the daily drudgeries of his clinic and laboratory to the places where his fellow scientists gather to present and discuss the results of their researches. Those who succeeded in getting leave to attend such meetings this year were offered the opportunity to listen to a generous selection of papers, most of them of high quality.

In mid-April, the Federation of American Societies of Experimental Biology met in Atlantic City. Abstracts of over 2000 papers (a record number) offered for the meetings of its 6 constituent societies were available beforehand, and from these anyone in attendance could easily pick as many from his sphere of interest as he could possibly listen to, even if he chose to spend his entire time attending meetings.

Two weeks later, while bacteriologists were gathered in Houston to listen to some 350 papers, the young clinical investigators who flocked in record numbers to Atlantic City were offered a selection of papers from about 450 titles and abstracts that were offered. Those charged with the duty of picking the hundred or so papers that were presented at the various meetings off the boardwalk must have had great difficulty in making the choices. Either that, or they showed unusually good judgment, for the addresses actually delivered were almost uniformly marked by a high degree of excellence both in content and in presentation.

Apart from listening to the actual reading of the papers, a function that could perhaps be served better by a perusal in their final published form, the most important function of these meetings consists in the small gatherings and discussions among those in attendance. The young investigators have opportunities to see, to hear and perhaps to meet the leading figures in their fields of interest, and the older and better established teachers and investigators have the opportunity to get a glimpse of the new crops of the young and developing scientists and to size up their own products as well as those of their colleagues. The social gatherings at these meetings serve fully as useful a purpose as the scientific sessions.

The generous support to medical research being given by various special agencies and to a rapidly increasing extent by federal agencies is without doubt responsible for much of the increase in the number and quality of the material being offered at these meetings. This is strikingly evident in the printed abstracts prepared by societies that permit the inclusion of acknowledgment of the sources of support for the studies being reported. The large and growing numbers of studies carried out with the support of funds from federal agencies is very impressive. Moreover, the federal institutions themselves are also beginning to reap a generous harvest as increasing numbers of papers of high quality are presented by workers at the National Institutes of Health, the Army Medical Center and the Veterans Administration hospitals among others.

For the hard-working doctor in practice there is a similar array of meetings, each of them attracting ever-growing numbers of people to their clinical and scientific sessions and many of them held during the spring and in pleasant surroundings. The American Medical Association, the state societies, the Colleges, Academies and other associations of clinical specialties all vie with each other to arrange attractive programs in their efforts to help the practitioners to keep in step with the rapid developments in the various fields. Here, too, there are ample opportunities to see the leading lights in medicine and hear what they have to say, as well as to meet old friends and make new acquaintances.

And the expenses, of course, are tax deductible.

HISTOPLASMOSIS IN NEW ENGLAND

THE importance and increasing recognition of histoplasmosis, particularly as a cause of pulmonary lesions that may simulate those of tuberculosis, have been discussed on various occasions in these columns, most recently in the issue of January 26.[1] The importance of exposure to acid soils contaminated with excreta of chickens or other birds was brought out at that time. A case of histoplasmosis in a native Vermonter who had never been outside New England was reported in the *Journal* in 1953,[2] indicating that, although most prevalent in the central states and along the Mississippi Valley, the causative fungus is also present in this part of the country.

Elsewhere in this issue of the *Journal*, Joress and Bushueff report further evidence of the occurrence and recognition of the disease among outpatients in the clinics of the Veterans Administration in Boston. These authors emphasize the value of the histoplasmin skin test and complement-fixation test of the serum for confirming the diagnosis of histoplasmosis in cases in which the disease is suspected on the basis of roentgenograms of the chest, and as an aid in the differential diagnosis of pulmonary tuberculosis.

REFERENCES

1. Editorial. Histoplasmosis: recent developments. *New Eng. J. Med.* **254**:185, 1956.
2. French, E. E., Jillson, O. F., and Crispell, L. S. Histoplasmosis in life-long resident of New England. *New Eng. J. Med.* **249**:270-272, 1953.

Plural Births.—*We know not whether the "baby-shows" have created a demand for human litters, but we have certainly remarked of late an unusual number of instances of three and four children at a birth.*

Boston M. & S. J. *June 12, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BLANEY — Cyril A. Blaney, M.D., of Westford, died on January 18. He was in his seventy-seventh year.

Dr. Blaney received his degree from Boston University School of Medicine in 1902. He was a former school physician in Westford and served on the Westford Board of Health up to the time of his death.

He is survived by two daughters and a son.

HILDRETH — Robert D. Hildreth, M.D., formerly of Westfield, died on April 20. He was in his seventy-fourth year.

Dr. Hildreth received his degree from Harvard Medical School in 1908. He was formerly associate medical examiner of the Westfield area and a member of the staff of Noble Hospital and was a fellow of the American Medical Association.

He is survived by his widow and two sons.

HURD — Randolph C. Hurd, M.D., of Newburyport, died on May 1. He was in his eighty-third year.

Dr. Hurd received his degree from Harvard Medical School in 1897. He was formerly chief-of-staff at Anna Jaques Hospital.

He is survived by his widow and four daughters.

CORRESPONDENCE

AMERICAN ASSOCIATION OF BLOOD BANKS

To the Editor: The ninth annual meeting of the American Association of Blood Banks will be held in co-operation with the sixth congress of the International Society of Hematology in Boston, September 3-5. During recent years the Association has become the leading organization for blood-bank workers in this country.

Everybody who participated in the 1955 annual meeting enjoyed the excellent scientific program, which included such guest speakers as Dr. R. R. A. Coombs, of Cambridge, England, and Dr. Ruth Sanger, of the Lister Institute in London.

The maturity of the Association is obvious to all who have been in close contact with it during the last couple of years.

The Association is one of the member institutions of the Joint Blood Council, Incorporated, which has recently been formed by the five national associations (American Association of Blood Banks, American National Red Cross, American Medical Association, American Hospital Association and American Society of Clinical Pathologists), principally concerned with obtaining, preserving, processing and distributing blood and blood derivatives.

We urge that everybody working with or interested in blood-bank problems join the Association. The office of the secretary is at 725 Doctors Building, 3707 Gaston Avenue, Dallas, Texas.

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Clinical Pathologist,
New England Baptist Hospital
MORTEN GROVE-RASMUSSEN, M.D.
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Children's Medical Center
MARK FALCON LESSES, M.D.
Blood-Bank Director,
Beth Israel Hospital

Boston

SUSPENSION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held May 10, 1956, it was voted to suspend the registration of Dr. Anthony S. Ripa, 1A Meridian Street, East Boston, for five months beginning July 1, 1956.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 10, 1956, it was voted to suspend the registration of Dr. Pasquale Costanza, 238 Maverick Street, East Boston, for five months beginning September 1, 1956.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 10, 1956, it was voted to suspend the registration of Dr. Joseph A. Famiglietti, 108 Meridian Street, East Boston, for five months beginning November 1, 1956.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEWS

Cancer Cells. By E. V. Cowdry. 4°, cloth, 677 pp., with 137 illustrations and 50 tables. Philadelphia: W. B. Saunders Company, 1955. $16.00.

In his impressive and almost encyclopedic presentation of the cancer problem, Cowdry has shown that his interest and knowledge of this rapidly expanding field is wider than might have been expected. Starting with a chapter devoted to the definition of the term cancer, he progresses to a discussion of the properties of malignant cells. The cytologic and histologic aspects of cancer cells are beautifully illustrated as is natural from one of our great microscopical anatomists. Much of the work presented is from his own laboratories, and it is interesting that, although he thinks that one may not be justified in so doing, one must attempt, as he does, to assess the cancer cell in terms of homologous normal cells, their growth and metabolism. The discussion of the biochemical aspects of cancer cells is disappointingly brief and does not achieve the high level of presentation of the earlier sections. That nucleic acids should be dismissed with a brief paragraph is most surprising. This first portion of the book comprises rather less than a third of the whole.

In succeeding chapters various aspects of knowledge concerning possible causative factors in the initiation of the cancerous process are presented. The discussion of the action of viruses as agents in the production of cancer is of considerable interest in the light of recent advances in ultra-thin sectioning technics for electron microscopy. Such technics have permitted the identification of viruslike particles in the cytoplasm of cells of a number of cancers. One inclines, even so, to agree with the author's conclusion that at present the thought that some human cancers may be caused by viruses is no more than an interesting possibility.

Much information is given on the susceptibility of normal cells to known carcinogens and the manner in which this process may be modified by such factors as age and sex. The problem of the latent period that is always observed in experimental carcinogenesis and its counterpart in industrial cancers in human beings is discussed. The geographic aspects of the cancer problem are presented, with a wealth of detail. Finally, brief sections on diagnosis, treatment and prevention conclude the clinical aspects of this book. The importance of cytologic and histologic examination of material from patients suspected of having cancer is suitably stressed for the establishment of an accurate diagnosis. In the present state of knowledge, it is essential that diagnosis in this disease be as accurate and complete as possible.

The final chapter on cancer research is of much interest even to those not in the field. Cowdry's remarks on the problem of support of cancer research can well be applied to

research in any field where temporary financing by yearly grants is likewise productive of feelings of insecurity on the part of the investigator.

The bibliography appended to this volume occupies slightly more than 62 pages of fine print. The number of references from 1954 is sizable. It is suggested that this will be one of the most useful sections of the book. *Cancer Cells* is beautifully printed on good paper. The reproduction of microphotographs is of high quality. The arrangements of the chapters into sections followed by a brief summary of the whole enables one rapidly to decide what portions are of interest so that this should prove a good reference work. It is unfortunate that the proof reading was not more carefully done; a number of printing errors are present that might well have been eliminated.

EDGAR B. TAFT, M.D.

The Health of the Elderly at Home: A medical, social and dietary study of elderly people living at home in Sheffield. By William Hobson, B.Sc., M.D., D.P.H.; and John Pemberton, M.D., M.R.C.P. In collaboration with E. R. Bransby, M.Sc., Ph.D.; H. Droller, M.D., M.R.C.P.; Cissie Roseman, B.Sc.; and D. L. Woodhouse, Esq. With a foreword by Lord Horder, G.C.V.O., M.D., F.R.C.P. 8°, cloth, 238 pp., with 12 illustrations and 82 tables. London: Butterworth and Company, Limited, 1955. 30 s.

This third in a series of studies on old people, supported by the Nuffield Foundation, achieves a more valid description than the other two — *Old People*, by Rowntree (1947), and *The Social Medicine of Old Age*, by Sheldon (1948). The authors, who are teachers of social and industrial medicine in the University of Sheffield, used a group of old people who had been the subjects of a social survey made by the Sheffield Council of Social Service in 1948, on whom they performed a fairly general physical examination, with a medical history, certain tests on urine and blood, dental examinations, ophthalmologic examinations, radiographic studies of the chest and thoracic spine and analyses of the diets.

The book has many admirable qualities. The exposition is confined to a precise statement of the revealed facts, with very little reference to medical literature and very brief discussions of the conclusions that can be drawn from the facts. The common sense and sound judgment of the general practitioners who made the clinical observations are commendable. There is an abundance of good sense and good taste. But it is difficult to define the audience that the book should reach. It is not for the general public or for workers in public health and social service, because it assumes thorough familiarity with clinical problems and does not describe individual cases or arrange massive solutions for their needs. All doctors who care for aging people should benefit greatly by it. Serious students of geriatrics can use it as a bare-bones guide.

The old people who were studied lived independently. They were not in hospitals or old-age homes or nursing homes, nor were they living with younger relatives. Thus, the book provides information on a segment of the important group of people who do not enter into descriptions of disease or even into statistical studies by teachers of medicine, whose observations are limited to institutionalized material. The prevalence of arteriosclerosis, hypertension, heart disease and many other chronic diseases in these "normal" old people is shown, and there is some evidence that they increase with advancing years. Geriatricians, aware of these facts, have hypothesized that disease has little to do, by and large, with how a man stands up to life. The authors strengthen this theory by showing that the "fitness" of these old people had little to do with disease and disability, whether they took the patients' opinion of their condition or the physicians' evaluations, or gave number and weight to the abnormalities. Roughly as many well-to-do were "fit" as were found among those living in poverty, and serious malnutrition cut across all classes. Psychologic, psychiatric and sociologic studies were not done. Perhaps they, with medical correlations, may show why and how some people cling to the independent management of their own lives to the end.

ROBERT T. MONROE, M.D.

Prolonged and Perplexing Fevers. By Chester S. Keefer, M.D.; and Samuel E. Leard, M.D. 8°, cloth, 248 pp. Boston: Little, Brown and Company, 1955. $5.50.

The diagnosis of prolonged fever has been for many medical generations a classic and, frequently, a frustrating clinical problem. In their aptly entitled volume the authors offer the clinician a guide to the solution of this problem.

The first part deals briefly with the physiology of temperature regulation and with febrile conditions arising from derangements of the central or peripheral mechanisms of temperature control. The second is devoted to fevers caused by infectious agents, and the third to noninfectious fevers. Each disease is introduced by a brief clinical description, with emphasis on diagnostic features and confirmatory tests and, usually, with relatively lengthy illustrative case reports. The diseases are grouped into frequent and infrequent causes of obscure fever, principal attention being paid to the former. In the authors' extensive experience, tuberculosis, local septic infections, rheumatic fever, brucellosis, enteric fever, malaria, tumors and blood dyscrasias are the frequent causes of this syndrome.

The authors have been successful in their evidently limited goal of presenting "the various means of establishing the diagnosis of prolonged fevers." The value of their book will be augmented if the reader supplements it with more systematic detailed discussions of pathologic entities, references to which may be found in good selection in the bibliography.

SIDNEY COHEN, M.D.

Diseases of the Ear, Nose, and Throat in Children. By T. G. Wilson, M.B., B.Ch., Litt.D., F.R.C.S.I., M.R.I.A. 8°, cloth, 307 pp., with 145 illustrations. New York: Grune and Stratton, Incorporated, 1955. $12.00.

With the exception of a book limited to otology in children published by Alexander of Vienna in 1917, this textbook by T. G. Wilson of Dublin is the first to deal exclusively with the diseases of the ear, nose and throat in children. As the scope and character of otolaryngological problems of infancy and childhood have increased considerably since 1917, the work on this subject is an important contribution from our European colleague.

The book is divided into six parts, which comprise diseases of the ear, speech defects, diseases of the nose, diseases of the pharynx, diseases of the larynx and diseases of the neck and thorax. There are 145 illustrations by the author, including seven pages of color plates.

Dr. Wilson has made the subject matter timely and up to date, not only by covering all types of infection in the upper and lower respiratory tracts but by including chapters on congenital abnormalities of the ear, nose and throat, deafness in childhood, auditory training, education and rehabilitation of the deaf child, speech defects and allergy.

In the preface, it is assumed that the readers already have a basic knowledge of anatomy and physiology, so that the author may devote himself to the problems specifically related to children. The book is concise but very informative, yet rather too short for a textbook in such an extensive field. Although it is comprehensive in its subject matter and inclusive of the more important and progressive points of interest in otolaryngology, it is inadequate in detail to fulfill its purpose completely. It is actually an outline. This is especially true of the treatments, most of which are covered in one short paragraph.

Specialists in the field may learn little that is new from this treatise, but will appreciate its practicality. To general practitioners, pediatricians and medical students, however, it should be of much interest and a good adjunct to a fuller text in otolaryngology. For them it will be a reference book

in which they can find an interesting, brief, and practical summary of child otolaryngology.

ELIZABETH DEBLOIS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Electrocardiography. Part 1. The Arrhythmias: With an atlas of electrocardiograms. By Louis N. Katz, M.D., director, Cardiovascular Department, Michael Reese Hospital, Chicago, and professorial lecturer in physiology, University of Chicago; and Alfred Pick, M.D., physician-in-charge of Heart Station and research associate, Cardiovascular Department, Michael Reese Hospital, Chicago. 4°, cloth, 737 pp., with 415 illustrations. Philadelphia: Lea and Febiger, 1956. $17.50.

Surgical Diagnosis. By Philip Thorek, M.D., professor of surgery, Cook County Graduate School of Medicine, clinical associate professor of surgery, University of Illinois College of Medicine, cosurgeon-in-chief, American Hospital, attending surgeon, Cook County Hospital, and senior attending surgeon, Alexian Brothers Hospital. 4°, cloth, 320 pp., with 291 drawings by Carl T. Linden, assistant professor of medical illustration, University of Illinois College of Medicine. Philadelphia: J. B. Lippincott Company, 1956. $12.00.

Atlas der Kolpomikroskopie. By Prof. Dr. Tassilo Antoine, and Priv.-Doz. Dr. Viktor Grünberger, I. Univ.-Frauenklinik, Vienna. 4°, cloth, 244 pp., with 176 illustrations. Stuttgart: Georg Thieme, 1956. DM 64.- $15.25. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Diseases of the Nervous System. By Sir Russell Brain, Bt., D.M. (Oxon.), P.R.C.P. (London), physician to the London Hospital and to the Maida Vale Hospital for Nervous Diseases, sometime neurologist to the Infants' Hospital and physician to the Royal London Ophthalmic Hospital, Theodore Williams Scholar in Physiology in the University of Oxford and Price Scholar in Anatomy and Physiology at the London Hospital. Fifth edition. 8°, cloth, 996 pp., with 90 illustrations. New York: Oxford University Press, 1955. $10.50. *(Oxford Medical Publications.)*

Urology. By B. G. Clarke, M.S., M.D., associate professor of urology, Tufts University School of Medicine, urologist, New England Center Hospital, urologist-in-chief, Boston Dispensary, and consultant in urology, Boston Floating Hospital; and Louis R. M. Del Guercio, M.D., assistant resident surgeon, St. Vincent's Hospital, New York City. 8°, cloth, 245 pp., with 162 illustrations and a frontispiece. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1956. $6.50.

Skin Surgery. By Ervin Epstein, M.D., assistant clinical professor of medicine (dermatology), Stanford University Medical School, chief of dermatology and syphilology, Highland-Alameda County Hospital, consultant, Oakland Area Veterans Administration Hospital, Mount Zion Hospital and Camp Parks Air Force Base Hospital, and member of the editorial staff of *Dermatologica.* 8°, cloth, 228 pp., with 101 illustrations and 2 tables. Philadelphia: Lea and Febiger, 1956. $7.50.

The Clinical Approach in Medical Practice. By G. E. Beaumont, M.A., D.M., F.R.C.P., D.P.H., Hon. consultant physician to the Middlesex Hospital, London, and to the Hospital for Diseases of the Chest, Brompton, London. 8°, cloth, 469 pp., with 74 illustrations. London: J. and A. Churchill, Limited, 1956. $9.00. (Distributed in the United States by Little, Brown and Company, Boston.)

Yellow Fever Vaccination. By Kenneth C. Smithburn, M.D., et al. 8°, paper, 238 pp., with 37 illustrations and tables. Geneva: World Health Organization, 1956. Clothbound, $5.00., £1.5s., or sw.fr. 15.- (Distributed in the United States by Columbia University Press, New York City.)

Strabismus: Diagnosis and treatment. By Beulah Cushman, M.S., M.D., attending ophthalmologist, Passavant Memorial Hospital, Swedish Covenant Hospital, Women and Children's Hospital, Chicago, and associate professor of ophthalmology, Northwestern University Medical School. 8°, cloth, 208 pp., with 11 illustrations. Philadelphia: Lea and Febiger, 1956. $6.00.

Neurochemistry. Edited by Saul R. Korey, M.D., professor of neurology, Albert Einstein College of Medicine of Yeshiva University, New York City; and John I. Nurnberger, M.D., research associate, Institute of Living, Hartford, Connecticut, and assistant clinical professor of medicine (neurology) and psychiatry, Yale University School of Medicine. With twenty-three contributors. 8°, cloth, 244 pp., with 29 illustrations and 40 tables. New York: Harper and Brothers, 1956. $6.75.

Fifth Annual Report on Stress. 1955-56. Edited by Hans Selye, M.D., Ph.D., D.Sc. (Hon.), F.R.S. (Canada), F.I.C.S. (Hon.), professor and director, Institut de Médecine et de Chirurgie expérimentales, Université de Montréal; and Gunnar Heuser, M.D. (Cologne), research associate and librarian, Institut de Médecine et de Chirurgie expérimentales, Université de Montréal. 8°, cloth, 815 pp., with illustrations and tables. New York: MD Publications, Incorporated, 1956. $20.00.

Pediatric X-Ray Diagnosis: A textbook for students and practitioners of pediatrics, surgery and radiology. By John Caffey, M.D., professor of radiology, Columbia University College of Physicians and Surgeons, attending pediatrician and roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City, consulting pediatrician, Grasslands Hospital, Westchester County, New York, and New Rochelle Hospital, New Rochelle, New York, consulting roentgenologist, Orange Memorial Hospital, Orange, New Jersey, and consultant in pediatric roentgenology, New York Hospital, New York City. Third edition. 4°, cloth, 1059 pp., with 1267 illustrations. Chicago: The Year Book Publishers, Incorporated, 1956. $28.00.

Formen des posttraumatischen Kopfschmerzes: Der neuralgische Schmerz. By Dr. Elmar E. Bues, lecturer in surgery and neurosurgery, University of Kiel. With a foreword by Prof. Dr. R. Wanke, Kiel. 8°, paper, 111 pp., with 28 illustrations. Stuttgart: Georg Thieme, 1956. DM 9.60.- $2.30. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Grosse Nervenärzte. Edited by Prof. Dr. Kurt Kolle, München. 8°, cloth, 284 pp., with 21 illustrations. Stuttgart: Georg Thieme, 1956. DM 29.40.- $7.00. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Exogene Faktoren in der Pathogenese der Poliomyelitis: Erläutert an dem Ergebnis von Untersuchungen während und nach der Epidemie in Nordrhein-Westfalen, 1952. By Doz. Dr. R. Ch. Behrend, Hamburg. 8°, paper, 98 pp., with 26 tables. Stuttgart: Georg Thieme, 1956. DM 14.40.- $3.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Klinik und Therapie der Vergiftungen. By Priv. Doz. Dr. Sven Moeschlin, lecturer, University of Zurich, and chief doctor, Medical Clinic, Bürgerspitals Solothurn (Schweiz). Second edition, revised. 8°, cloth, 521 pp., with 64 illustrations. Stuttgart: Georg Thieme, 1956. DM 59.- $14.05. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Festschrift zum 70. Geburtstag von Prof. Dr. Dr. h.c. Max Bürger. Edited by Prof. Dr. Josef Nöcker, physician-in-chief, Medical University Clinic, Leipzig. 4°, cloth, 191 pp., with illustrations and tables. Leipzig: Georg Thieme, 1955. DM 27.50.-

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Differentialdiagnose innerer Krankheiten: Eine kurzgefasste Darstellung für Ärzte und Studierende. By Dr. Robert Hegglin, lecturer, Universität Zürich, and head doctor, Medical Clinic, Kantonsspitals St. Gallen. Fourth edition, improved and enlarged. 8°, cloth, 678 pp., with 372 illustrations and 17 tables. Stuttgart: Georg Thieme, 1956. DM 69.60.- $16.55. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Röntgenaufnahmetechnik in der Hals-Nasen-Ohrenheilkunde. By Dr. med. Burkhard Schlosshauer, Hamburg. 4°, cloth, 48 pp., with 72 illustrations. Stuttgart: Georg Thieme, 1956. DM 12.- $2.85. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

NOTICES

ANNOUNCEMENT

Dr. Lester H. Tobin announces the removal of his office for the practice of internal medicine to 84 Humphrey Street, Swampscott, Massachusetts.

SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at Prendergast Preventorium, 1000 Harvard Street, Mattapan, on Tuesday, June 19, at 12 noon.

Dr. Herbert J. Kaufman will talk on "Progress in the Treatment of Primary Tuberculosis." All physicians are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

June 8. International Medical-Surgical Meetings. Page 540, issue of March 15.
June 8–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
June 8–10. American College of Chest Physicians. Page 876, issue of May 3.
June 9 and 10. Society for Investigative Dermatology. Page 876, issue of May 3.
June 10 and 11. American Gastroscopic Society. Page 875, issue of May 3.
June 11. American Physicians Fellowship Committee of Israel Medical Association. Page 1051, issue of May 31.
June 15. New England Pediatric Society. Page 924, issue of May 10.
June 17. American Electroencephalographic Society. Page 924, issue of May 10.
June 18–20. American Neurological Association. Page 875, issue of May 3.
June 18–22. Medical Library Association. Page 1051, issue of May 31.
June 19. South End Medical Club. Notice above.
June 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
June 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.
July 9. Fifth Annual Symposium for General Practitioners. Page 1010, issue of May 24.
August 19–23. American College of Chest Physicians. Page 840, issue of November 10.
September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
September 10–14. American Dietetic Association. Page 1180, issue of December 29.

Calendar for the Week Beginning Thursday, June 14

Thursday, June 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Pathogenesis of Atherosclerosis. Dr. Edward B. Hager. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

Friday, June 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

Saturday, June 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.

(Concluded on page xxvi)